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Romanian Journal of Military Medicine

REVISTA DE MEDICINĂ MILITARĂ

- *The Medical-Military Institute: Its past and its future*
- *Evolution of mortality rates in ST elevation myocardial infarction*
- *Gingival involvement of oral non-tumoral mucosal diseases*
- *Emerging concepts regarding the molecular profile of breast carcinoma: one-year experience in a University Center*
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Contents

EDITORIAL

Mihail Tudosie

- ***The Military-Medical Institute: Its past and its future*** **5**

REVIEW ARTICLE

Alice E. Munteanu, Cristina M. Calcan, Irina Florescu

- ***Evolution of mortality rates in ST elevation myocardial infarction*** **7**

Elena C. Tofan, Ioanina Părlătescu, Elena Coculescu, Şerban Ţovaru, Carmen Nicolae, Bogdan I. Coculescu

- ***Gingival involvement of oral non-tumoral mucosal diseases*** **11**

Oana C. Voinea, Maria Sajin, Adrian V. Dumitru, Oana M. Pătrașcu, Tiberiu A. Georgescu, Monica M. Cîrstoiu, Dan C. Jinga, Adriana E. Nica

- ***Emerging concepts regarding the molecular profile of breast carcinoma: one-year experience in a University Center*** **17**

SYSTEMATIC REVIEWS, META-ANALYSIS

Octavian Vasiliu, Daniel Vasile, Andreea F. Făinărea, Mihaela C. Pătrașcu, Elena A. Morariu, Raluca Manolache, Iulia Alexandru, Flavius T. Androne

- ***Analysis of risk factors for antipsychotic-resistant schizophrenia in young patients – a retrospective analysis*** **25**

ORIGINAL ARTICLES

Mirela Radu

- ***Blending between occultism and scientism in Vasile Voiculescu's short stories*** **30**

Lucia E. Ionescu, Viorel Ordeanu, Manuel Dogaru, Marius Necșulescu, Diana M. Popescu, Simona N. Bicheru, Gabriela V. Dumitrescu

- ***Research for the development of logistics planning information support in health protection against biological agents*** **36**

L. Eftimie, R. Hristu, Marius Dumitrescu, Mariana Costache, S. G. Stanciu, M. Sajin, G. A. Stanciu

- ***Modern methods to differentiate benign thyroid nodules from malignant ones*** **40**

CLINICAL PRACTICE

Radu A. Macovei, Radu C. Ţincu, Mihail S. Tudosie

- ***Association of rare disease and acute intoxication – case report*** **46**

A.M.C. Țâncu, E. Preoteasa, C. Preoteasa, M. Pantea, M. Meleșcanu Imre
- ***Clinical aspects in implant fixed prosthodontics oral rehabilitation. Case report*** **50**

Carmen A. Sîrbu, Octavian M. Sîrbu, Alexandra E. Bastian
- ***Occipital radionecrosis and neuroplasticity in astrocytoma. Case report*** **54**

ADMINISTRATIVE ISSUES

Guidelines for authors **60**

ROMÂNIA
MINISTERUL APĂRĂRII NAŢIONALE

Atestat

Ministrul apărării naţionale

dorind a răsplăti meritele

redacţiei pubilcaţiei „Revista de Medicină Militară",

în semn de apreciere a contribuţiei avute la creşterea prestigiului structurilor medicale din Armata României, cu ocazia aniversării a 120 de ani de la înfiinţare,

conferă ***Emblema de Onoare a Armatei României***
-cu însemn de pace-

Acordat în Bucureşti, 15 Noiembrie 2017

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Atestat E.O.A.R./nr.1

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EDITORIAL

The Military Medical Institute: its past and its future

Mihail Tudosie

Col. Lect. MIHAIL TUDOSIE

Commander in Chief, Military Medical Institute, Bucharest, Romania

The Military-Medical Institute was founded in 1884 through High Royal Decree number 2824 published in Official Monitor number 2/23.01.1884, and was initially led by general academician Zaharia Petrescu. For a long period of time, the institute functioned based on models such as similar Austrian and Prussian institutes, but with a strong French influence. In those times, as well, the students attended both professional training courses at the Faculty of Medicine of Bucharest and military medical training within the Institute.

Through a regrettable decision of the authorities, the courses of the institute are suspended in 1987, military medicine being deeply prejudiced. During the following years, up to 1990, military medical staff was recruited indirectly.

In 1990, the Government of Romania brings moral justice, by adopting Government Decision 585, through which the Military-Medical Institute of Bucharest is re-established as a superior institute of military medical education, with a Military-Medical Training Section based in Târgu-Mureş.

The present activity of the Institute relies on these traditions, which ensure military medical training of all future doctor officers of the Romanian Army, the Ministry of Internal Affairs and the National Administration of Prisons.

For the continuous improvement of military doctors in the structures of the Romanian Army, career classes are being organized and held in the Military-Medical Institute with a curricula that is compatible with NATO standards within the operational medicine field.

The teaching personnel of the Institute is permanently preoccupied with promoting academic elitism. Students must find models to follow. Every day, the teaching personnel of the Institute must pass the test of education optimization and of increasing the quality of the educational act. In this regard, steps are being taken at the ministry's management level for the recruitment of teaching personnel. The quality of the educational act can be improved only through the recruitment of personnel with a high level of professional training and, also, through the equipment of classrooms with video projection systems and highly performing apparatus in both Bucharest and Târgu-Mureş,

Because mobility nowadays is not only desirable, but also a necessity, we are doing all that is in our power to achieve this scope. Our students participate in Erasmus+ programs offered by the two Universities of Medicine and Pharmacy – "Carol Davila" of Bucharest and that of Târgu-Mureş – with whom we form a partnership. These scholarships ensure our students' preparation for a whole semester at first class

European medicine universities. Thus, students connect “live” to medicine in other countries. At the national level, they participate in the experience exchange program held between civil universities – TransMed. Military students are amongst the most disciplined and diligent, representing a true heraldry of the Army in the civil universities’ environment.

Also, regarding operational military medicine, our students have participated and continue to participate in different national and international exercises, where they learn from the experience of NATO allied countries. A lot of students of the Institute work during their studying years as volunteers at emergency medicine services, such as S. M. U. R. D.

In order to improve scientific performances, the Military Medicine Students’ Association, in collaboration with the Military-Medical Institute, annually organizes a scientific presentations event, in partnership with military students of other academies. In a similar manner, UMF Tg. Mures annually organizes an international congress, which includes a special military medicine session.

A reason for pride is also represented by the consistent participations of the institutes’ students at numerous meetings, symposiums and congresses organized by the civil medicine universities or by the army: The Balkan Medicine Congress or the congresses organized by the academies representing the three forces of the Romanian Army. Thus, young military students are connected to a flow of information pertaining to university science, showing a striking inclination towards research work.

Another aspect pertaining to priority preoccupations is represented by the participation in sports activities organized between military education institutes or between the various components of the National Defense System, Public Order System and National Security System, where the students of the Institute always win a leading place.

Taking into consideration the actual recruiting demands of the Army, regarding the increase of our defense capability, the tuition figures for 2018 have doubled. Thus, 100 places were approved for Bucharest and another 100 places for Tg. Mures. Of these, general medicine represents 60 places in Bucharest and 90 in Tg. Mures. For dental medicine, 13 places are approved, and 15 for pharmacy, only in Bucharest. The other beneficiaries have their places approved for general medicine and dental medicine as follows: Ministry of Internal Affairs – 12 places (7 in Bucharest and 5 in Tg. Mures), and National Administration of Prisons - 8 places for general medicine (5 places in Bucharest and 3 in Tg. Mures), 2 places for dental medicine. As tuition figures rise, by the order of the Ministry of National Defense, in 2018, the institute has 20 places approved for doctors who will become officers through indirect activation.

For all the conducted activities, we enjoy an excellent collaboration with military hospitals and operative military units, as well as with civil universities. Thus, we can form and perfect military doctors for our hospitals and units, who are always ready to take part in international missions.

It is known that the performing armies of the world have never hesitated to show their skill, equipment and combative force. We also adhere to this direction, going out in public space every time we have the chance.

The image of the Institute if promoted by all means (press, radio, television, Internet). The students of the Institute participate in military ceremonies, charity events or blood donating activities, and activities which promote the military doctor profession in civil and military high-schools.

In the future, we wish to maintain and even ascend this standard of medical and military training through which our students have always stood out. We will stress the importance of developing the capacity and appetite for learning, of creativity, and of creating the profile of a military doctor that is receptive to all that is new, always willing to be involved, ready for action, competent and competitive. The future belong to these young people and for this, we do all that is in our power to form them as medical doctors of great value for the Romanian Army.

REVIEW ARTICLE

Article received on April 21, 2017 and accepted for publishing on September 18, 2017.

Evolution of mortality rates in ST elevation myocardial infarction

Alice E. Munteanu[1,2], Cristina M. Calcan[1], Irina Florescu[2]

Abstract: *The purpose of this paper is to provide information about mortality rate in patients undergoing primary angioplasty for STEMI. Cardiovascular diseases lead to one third of the deaths worldwide, surpassing the mortality rate produced by neoplasia, acute respiratory failure and diabetes mellitus all together. In the world, approximately 17 million die annually because of cardiovascular disease and every 5 seconds one is suffering from a myocardial infarction.*
In 2010, in our country was implemented a national program (RO-STEMI) to offer rapid interventional treatment for patients with STEMI, aligned to ESC Guidelines. At the beginning only small parts of the patients were transferred to the hospital in charge for STEMI, so, we chose to study patients from the second year of the program and from last year. We made a retrospective study, including patients with STEMI that reached our hospital for primary angioplasty in the first 12h after the debut of the symptoms, aiming to make a parallel between the in-hospital mortality rates at maximum one month after the primary PCI. In order to be included, the patients must present ST elevation and another 1 out of 3 criteria (clinical, echocardiographic and biological changes suggestive for myocardial infarction).
The main target was to evaluate the evolution of early mortality rates post primary PCI after the changes in the ESC Guidelines and the progresses in the medical field. A secondary target was to correlate mortality rates with the presence of comorbidities or risk factors.

INTRODUCTION

Alexander Muirhead is reported to have attached wires to a feverish patient's wrist to obtain a record of the patient's heartbeat in 1872 at St Bartholomew's Hospital.[1]

Another early pioneer was Augustus Waller, of St Mary's Hospital in London.[2] His electrocardiograph machine consisted of a Lippmann capillary electrometer fixed to a projector. The trace from the heartbeat was projected onto a photographic plate that was itself fixed to a toy train. This allowed a heartbeat to be recorded in real time.

An initial breakthrough came when Willem Einthoven, working in Leiden, the Netherlands, used the string galvanometer (the first practical electrocardiograph) he invented in 1901.[2]

This device was much more sensitive than both the capillary electrometer Waller used and the string Galvanometer that had been invented separately in 1897 by the French engineer Clément Ader.[3]

Einthoven had previously, in

[1] Carol Davila University Central Emergency Military Hospital, Bucharest
[2] Titu Maiorescu University, Faculty of Medicine, Bucharest

1895, assigned the letters P, Q, R, S, and T to the deflections in the theoretical waveform he created using equations which corrected the actual waveform obtained by the capillary electrometer to compensate for the imprecision of that instrument. Einthoven also described the electrocardiographic features of a number of cardiovascular disorders. In 1924, he was awarded the Nobel Prize in Medicine for his discovery.[3] In 1937, Taro Takemi invented the first portable electrocardiograph machine.[4]

Cardiovascular diseases represent the main cause of death worldwide, 30% of them being caused by coronary artery disease. Myocardial infarction (MI) is one of the five main manifestations of coronary heart disease, namely stable angina pectoris, unstable angina pectoris, MI, heart failure and sudden death.[5]

Myocardial Infarction (MI) is defined by myocardial cell necrosis due to significant and sustained ischemia. Most frequently it is an acute manifestation of atherosclerosis-related coronary heart disease. MI results from either coronary heart disease, which implies obstruction to blood flow due to plaques in the coronary arteries or, much less frequently, to other obstructing mechanisms (e.g. embolism, spasm of plaque-free arteries).[6]

The clinical presentation of MI varies from a minor coronary event to life-threatening clinical situations or sudden death.[2] The criteria for STEMI are well known – specific, prolonged >15-20 min pain, specific site, and it is not ameliorated by nitroglycerin intake. The ECG shows persistent ST elevation or new onset of LBBB. Specific biomarkers are represented by high-sensitive Troponin I, CK/CK-MB, which have a specific dynamic curve.[7]

In 2010 in our country debutantes a national program named ”RO-STEMI”. In this program all patients with STEMI, from a well-defined area, are send to a certain hospital for being coronarographic evaluated. Due to this program more than 63% of patients’ beneficiated of myocardial reperfusion and the mortality rate dropped all over the country from 13 to 7%.[8]

MATERIALS AND METHODS

It’s been realized a retrospective study in STEMI patients in our hospital, on all patients from 2012 and 2016. All the patients included in this study respected STEMI criteria for diagnosis. We took 252 patients from 2012, out of which 29% were women and 71% were men, and 136 from 2016, with a non-significant difference in gender balance (28% women and 72% men). The number of patients is smaller in 2016 than in 2012 because in the beginnings of the national program there were only a small number of hospitals being part of it. In present the number of STEMI hospitals has increased so STEMI patients are distribute to more STEMI centers than during the past years.

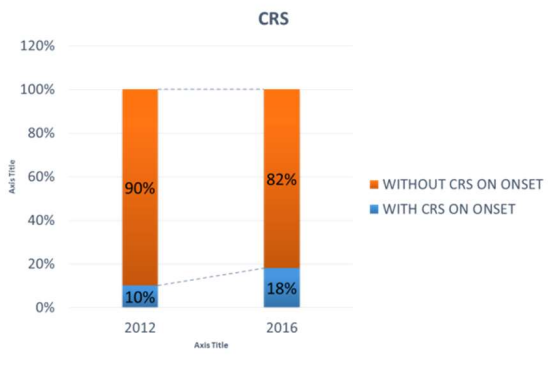
RESULTS

During this period of time, the median age of suffering an infarction was 60 years for men, with no significant difference between years, but for women the age evolved, so now, usually women suffer a myocardial infarction at about 63, compared with 66 years old in 2012.

The onset can be seen as a predictor for evolution and a gravity factor for STEMY patients.

A cardiorespiratory stop onset represents a high gravity risk factor. We noticed that in 2016 were twice more patients, than 2012, with cardiorespiratory stop on onset of STEMI. Knowing that, it is expected that the mortality rate being higher in 2016 that 2012.

Figure 1 Distribution of patients by cardiorespiratory stop onset.



The distribution of modifiable risk factors is the same for the 2 groups, the change consists of the number of risk factors present at the same patient, which was

definitely higher last year (in average 2 risk factors per patient in 2012 vs. average 3.5 risk factors/patient in 2016). Even if we strongly advise the patients to quit smoking, and there is also a huge implication of the government in this, the number of smokers increased, but the good news is that their mortality has a decreasing trend over the years.

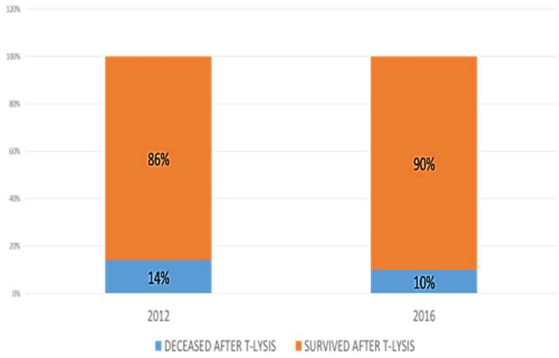
The median time from pain to cath-lab has lowered from 12h in 2012 to 9h in 2016. This improvement could be in one side due to well function of RO-STEMI program, and in other side due to improvement in social health education, the patients being better informed about myocardial infarction symptom-tology which decrease pain-call time.

If we take a look to the coronary lesions, we can see that first affected artery is left anterior descending artery (LAD), followed by right coronary artery (RCA), circumflex artery and marginal artery.

A very important observation is the growth of the number of patients with right coronary artery involvement, with can be associated with right ventricle infractions and an extremely poor prognosis. Also right coronary artery involvement means a higher risk of malignant arrhythmias and sudden cardiac death. 45% of STEMI patients had only one affected vessel, 40% had 2 affected vessels and only 15% had three coronary arteries affected most of them with CABG indication.

Only 15% of the patients in 2012 were thrombolysed before PCI, while in 2016 the use of t-lyse increase to more than 30% of the patients, this measure helps physicians to buy time for them to reach the cath lab.

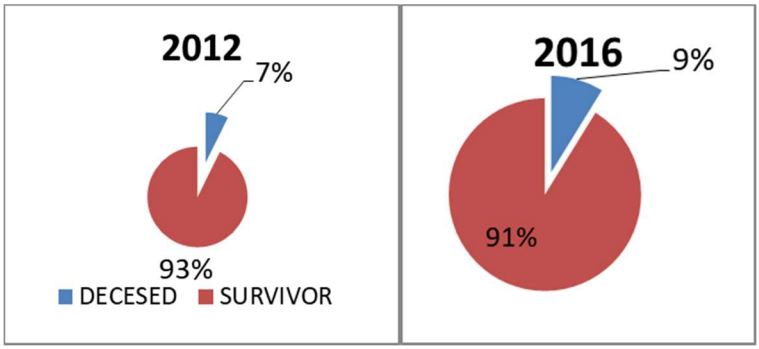
Figure 2 Rate of deceased after thrombolysis



From the number of those thrombolised, only a small amount has died, but none because of a bleeding. All died because of malignant arrhythmias or asystolia secondary to the myocardial infarction. Notice that in 2016, even though the number of thrombolised patients was bigger than in 2012, the rate of deceased patients after thrombolysis was smaller in 2016 than in 2012. The reason for this difference could be a better triage of elected patients and the evolution of thrombolytic agents.

At the beginning, drug eluded stents were extremely rare and expensive, nowadays we use much more frequently DES then bare metal stents, in 2016 73% of used stents were DES and the target is using only DES, as the indication in ESC guideline.[7] This made the rate of early in stent restenosis to go from almost 20% to 0%.

Figure 3 Mortality rate in the two groups of patients



Due to the shortening of the time from symptoms-onset to revascularization and from associating more frequently thrombolysis with PCI, the number of those with ventricular dysfunction has dropped significantly.

Even though the number of thrombolysis raised, and the time to cath lab is shorter, the number of patients who didn`t make it to the cath lab is increasing, the mortality rate has increased from 2012 to 2016. If we consider that the rate of cardiorespiratory stop as onset as a high gravity factor and if we see that the patients in 2016 were more complex than in 2012, then the high mortality rate is expected. Another factor suggests that the gravity of cases was higher in 2016 is that the number of deceased patients without reperfusion was higher in 2016.

CONCLUSIONS

The National Program RO-STEMI became more effective by increasing the number of involved hospitals.

During time the mortality rate have had a slightly increasing trend due to a growth of the number of risk factors/patient, an increase in the severity of the coronary lesions, an increase in the number of the lesions in the right coronary artery, and a poorer prognosis in echocardiography.

The time from symptoms onset to cath lab decreased and by associating more frequently thrombolysis for "buying" more time, so the chances for the ventricle to remodel remain low.

By respecting the ESC guidelines for each period of time, even though the early mortality rate seems to have an ascending trend, the overall mortality rate and longtime prognosis of the STEMI patients are getting better.

It is very important to make such an analysis from time to time, in order to make thinks go better and see where some changes could be made.

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REVIEW ARTICLE

Article received on November 09, 2017 and accepted for publishing on February 28, 2018.

Gingival involvement of oral non-tumoral mucosal diseases

Elena C. Tofan[1], Ioanina Părlătescu[1], Elena Coculescu[1], Şerban Ţovaru[1], Carmen Nicolae[1], Bogdan I. Coculescu[2]

Abstract: *Gingival conditions are frequently encountered in dental clinical practice and they can raise diagnosis and treatment problems. The diagnostic is variable from normal conditions to autoimmune diseases or even malignancy. Some of them cause disturbances such as pain, burning sensation and have an impact on patient's quality of life.*

INTRODUCTION

Although oral cavity is an area easy to explore by visual exam, there is a large variety of conditions and disorders which can be encountered. We present a general overview of gingival lesions frequently associated with oral mucosal diseases. Dental plaque-induced gingivitis and all gingival enlargements (reactive or tumorous with benign, cystic or malignant variants) are not the subject of this article.

DEFINITION OF SPECIFIC TERMS AND LESIONS

The gingiva is a "first line" mechanical barrier defined as the keratinized mucosa that covers the teeth and the alveolar bone. The periodontium is made of gingiva with the alveolar bone, periodontal ligament and cementum. The mucogingival junction separates the gingiva from alveolar mucosa [1]. In healthy persons the gingiva has a pink color (Figure 1), or it can have pigmented areas depending on the individual skin color (Figure 2).

Histologically, gingiva is composed of a thick stratified, keratinized epithelium and the underling connective tissue made of collagen and elastin fibers, fibroblasts, melanocytes and immune cells [2]. The epithelium cell-to-cell adhesion is done through desmosomes and adherence junctions while the adhesion to the basement membrane is done by hemidesmosomes and focal contacts [3].

Superficial lesions affect epithelium and underlying connective tissue. Depending on the clinical appearance, evidenced by visual examination, they can be divided into: keratosis or white lesion (Figure 3A and 3B), atrophic (Figures 4A, 4B, 4C), ulcers resulting from vesicles (Figure 5A) or bulla (Figure 5B).

The gingival diseases are presented in the periodontal diseases classification elaborated by Armitage in 1999 [4] which is universally

Corresponding author: Ioanina Părlătescu
ioaninap@yahoo.com

[1] Oral Medicine/Oral Pathology Discipline, Faculty of Dental Medicine, University of Medicine and Pharmacy Carol Davila, Bucharest

[2] Department of Anti-infective Medical Protection and Epidemiological Alerts, Center for Military Medical Scientific Research, Bucharest, Romania

accepted for both periodontal and gingival conditions.

Figure 1. Normal gingiva

Figure 2. Pigmented gingiva

Figure 3A. Gingival white lesion. Extended homogenous plaque of unknown etiology. Diagnosis: leukoplakia

Figure 3B. Gingival white lesion. Diagnosis: traumatic keratosis (associated with aggressive tooth-brushing technique)

Figure 4A. Mild atrophy. Diagnosis: desquamative gingivitis in oral lichen planus

Figure 4B. Moderate atrophy. Diagnosis: desquamative gingivitis in oral lichen planus

Figure 4C. Severe atrophy and reticular keratosis. Diagnosis: desquamative gingivitis in oral lichen planus

Figure 5A. Small gingival ulcers following vesicles. Diagnosis: primary herpetic gingivitis

Figure 5B. Extended ulceration after bullae rupture. Diagnosis: desquamative gingivitis in bullous dermatosis

The gingival disorders are presented in Table 1.

CLINICAL FEATURES AND THE BASIC THERAPEUTICALLY APPROACH OF ORAL MUCOSAL DISEASES WITH GINGIVAL INVOLVEMENT

We reviewed and summarized the clinical characteristics of the most frequent oral diseases. The oral manifestations of general diseases cover a large range of conditions (Table 2). The mainly local signs usually affects more than one mucosal area, so the gingival lesions must be interpreted in the whole context.

Table 1. The gingival diseases classification [4]

Periodontal diseases classification. Section gingival diseases		
A. Dental plaque-induced gingival diseases	1. Gingivitis associated with dental plaque only 2. Gingival diseases modified by systemic factors 3. Gingival diseases modified by medications 4. Gingival diseases modified by malnutrition	
B. Non-plaque-induced gingival lesions	1. Gingival diseases of specific bacterial origin 2. Gingival diseases of viral origin 3. Gingival diseases of fungal origin	
C. Gingival lesions of genetic origin	1. Hereditary gingival fibromatosis 2. Other	
D. Gingival manifestations of systemic conditions	1. Mucocutaneous disorders	1) lichen planus 2) pemphigoid 3) pemphigus vulgaris 4) erythema multiforme 5) lupus erythematosus 6) drug-induced 7) other
	2. Allergic reactions	
E. Traumatic lesions (factitious, iatrogenic, accidental)	1. Chemical injury 2. Physical injury 3. Thermal injury	
F. Foreign body reactions		

Oral lichen planus is a disease with chronic evolution and immune mediated pathogenesis [5]. The clinical signs and symptoms are variable depending on the lesions associated [2]. The lesions are multiple, associated, merged and coexist and symmetrically distributed. The gingival involvement, commonly encountered in these patients is described as desquamative gingivitis. This shows various lesions from white, keratotic to atrophy, ulcerations and bullae. The diagnostic criteria universally accepted includes the histological confirmation (with hydropic degeneration and band-like T-cells infiltrate), although there are microscopic features similar to other mucosal diseases [6].

The therapy is not curative but it intends to control acute lesions and symptoms. The agents used cover a large spectrum of drugs: topical or systemic corticoids, hydroxychloroquine, azathioprine, mycophenolate mofetil, methotrexate, dapsone, thalidomide, biological agents etc. [6].

Mucous membrane pemphigoid is a chronic

autoimmune blistering disease which presents subepithelial vesicles and bullae. Any area of the oral mucosa can be affected. The gingival lesions present as desquamative gingivitis which simulates oral lichen planus and are noticed in 60% of cases [6]. The diagnosis is established by histopathological analysis and direct immunofluorescence which shows along the basal membrane linear deposits of immune-globulin IgG, IgM, IgA and complement [6]. The therapy is mainly long-term immunosuppressive treatment used local and systemic.

Table 2. General data on oral mucosal diseases, clinical features [1-3]

Oral conditions	Disease	Oral mucosa manifestations
Autoimmune diseases	Oral lichen planus	Variable presentation, generally symmetrical lesions (reticular, popular, plaque form, atrophy, ulcers, bulla)
	Pemphigus vulgaris	Small intraepithelial bulla and secondary erosion
	Mucous membrane pemphigoid	Desquamative gingivitis, shallow ulcer after multiple blisters affecting the oral mucosa
	Linear IgA dermatosis	Annular vesicular-bullous lesions
	Allergic reaction to dental materials and/oral health products	Variable clinical features: inflammation, reddish or white areas
Infectious diseases		
Viral	Primary herpetic infection	Ulcerative lesions following short duration vesicles
	Secondary herpetic infection	
	Herpes zoster	Unilateral ulcers following vesicles, located along nerve distribution, mainly in older patients
Bacterial	Necrotizing ulcerative gingivitis	Painful, purulent ulcers of the gingival papillae; mostly in teenagers and young adults
Traumatic lesions	Caused by excessive tooth brushing	Ulcers, atrophy and keratosis
	Mucosal burn caused by substances held in close contact for a long period of time	
	Local radiotherapy	
Pigmented lesions	Rasial pigmentation	Pigmented areas on the gingiva
	Melanotic macule	
	Metallic tattoo	
White lesions	Leukoplakia	Predominantly white lesion of unknown or tobacco etiology

Oral pemphigus vulgaris is a lifelong autoimmune bullous disease which affects the epithelium with autoantibodies directed against the desmosomal cadherine – desmoglein 3 causing acantholysis and blistering [7]. Oral mucosa is the initial site of the lesions in 80% of the patients [7]. The painful, irregular-shaped erosions and blisters affect the buccal mucosa, the tongue and gingiva. In these patients the desquamative gingivitis shows ulcers following bullae. The diagnosis is established by clinical features, histopathology, immunopathology, and serology. Direct immunofluorescence shows intercellular deposition of immunoglobulin G and complement 3 [7]. Treatment is complex and includes a variety of immunosuppressive and anti-inflammatory steroids in order to get disease control.

In patients with desquamative gingivitis there is an increased risk periodontal tissue breakdown mainly caused by the plaque deposits and the pain associated with tooth-brushing [8].

Herpetic oral viral infection is caused by two types of herpes simplex virus. The primary infection which affects mainly children or young adults shows a wide range of manifestations varying from an extended oral vesicular-ulcerative eruption to a reduced, asymptomatic condition [2, 9]. The primary eruption may be associated with general signs and symptoms such as fever, malaise, lymphadenopathy and dysphagia. The secondary infective episode usually involve gingival mucosa and the hard palate. The lesions are vesicles which break quickly and leave painful ulcers. These heal in 7-10 days without scars [9] in healthy and immunologically competent patients. Infections diagnosed early show a good response to antiviral medication. Also local symptomatic suspensions will ease the discomfort in both primary and secondary herpetic eruption.

For **pigmented lesions of the oral cavity**, more than for other conditions the diagnosis is challenging even for an experienced clinician [10]. On the gingiva the physiological pigmentation and the melanotic macules are frequently seen but this does not exclude a melanoma or Kaposi sarcoma diagnosis. The physiological pigmentation is caused by an increased melanin pigmentation of the basal layer or incontinent melanin and/or melanophages in the superficial lamina propria and the melanotic macules are a result of a increased melanin production from the basal melanocytes. In these cases, the diagnosis is appreciated after size, shape, or color, location together with the anamnestic data [10]. Generally a biopsy is needed to determine a definitive diagnosis and to exclude risky conditions.

Oral leukoplakia is defined as a predominately white lesion of the oral mucosa, lesion of questionable risk having excluded (other) known diseases or disorders that carry no increased risk of cancer [11]. It can be met in any area of the oral mucosa, including gingiva. At present about this lesion, the literature states that neither histology nor clinical factors can reliably predict the behavior [12]. Proliferative verrucous leukoplakia is one of the most aggressive form described which shows a predominant gingival involvement.

CONCLUSIONS

These gingival conditions can share similar clinical features which may lead to misdiagnosis or underdiagnosed situations. Dentists and general practitioners need to be familial to the gingival disorders. In general a definitive diagnosis is based on biopsy of the lesional tissue but also the anamnestic data should be taken to account.

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REVIEW ARTICLE

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Emerging concepts regarding the molecular profile of breast carcinoma: one-year experience in a University Center

Oana C. Voinea[1,2], Maria Sajin[1,2], Adrian V. Dumitru[1,2], Oana M. Pătrașcu[1,2], Tiberiu A. Georgescu[1,2], Monica M. Cîrstoiu[1,3], Dan C. Jinga[1,4], Adriana E. Nica[1,5]

Abstract: *Breast carcinoma represents the leading cause of oncologic mortality for women. Due to therapeutic and diagnostic advances, the mortality and morbidity in the last decade declined, but breast cancer still has a great impact on quality of life and also on medical service cost. In the light of these facts, an integrated approach, considering histopathology features, molecular profiles and corroboration with clinical and imagistic data is necessary. A descriptive retrospective one-year study analyzed the breast cancer heterogeneity in 121 cases registered in the Pathology Department of the University Emergency Hospital in Bucharest, Romania. Our purpose was to evaluate histopathological, immunohistochemically, clinical and imagistic aspects of breast cancer considering the current molecular classification (Luminal A, Luminal B, HER2 enriched and triple negative/basal like).*

Our assay revealed that most prevalent histotype was NST (no special type) followed by invasive lobular carcinoma. Considering the molecular pattern, the most common was luminal B. Triple negative basal like and HER 2-enriched were correlated with an aggressive morphologic pattern and lymph-nodes positivity. Considering the imagistic acquisitions, mammography proved to be the most accurate technique for measuring the dimension of NST.

In conclusion, breast carcinoma is a heterogeneous disease that needs an integrated approach and personalized treatment based on the histopathologic and molecular features. Considering the great number of advanced stages as diagnosis, a national screening program for breast cancer is imperiously needed.

Keywords: *breast cancer, NST, ILC, IHC, molecular subtypes, biopsy*

[1] The "Carol Davila" University of Medicine and Pharmacy Bucharest, Romania

[2] Pathology Department of University Emergency Hospital, Bucharest

[3] Department of Obstetrics and Gynecology of University Emergency Hospital, Bucharest

[4] Oncology Department of University Emergency Hospital, Bucharest

[5] Department of Anesthesiology and Intensive Therapy of University Emergency Hospital, Bucharest

INTRODUCTION

According to the most recent statistic database of WHO 2015, breast carcinoma represents the main cause of mortality for Romanian women [1]. The decline of breast cancer mortality is a trend that, according to the most recent epidemiologic estimation will continue [2]. This direction is mostly due to advancement in diagnosis and treatment [3].

A better understanding of pathogeny and a more accurate diagnostic approach of breast cancer led to several updates in guidelines for classification and treatment. Since 2003, for grading breast carcinomas, the Elston Ellis semiquantitative method modified score was used according to the 3rd edition of WHO guidelines for classification the breast tumours. The most recent WHO diagnos-

tic guideline (4th edition, 2014) considers that for prognostic and predictive factors a panel of antibodies is needed for a further classification into molecular subtypes (luminal A, luminal B, Her2 enriched and triple negative basal-like). This approach is supported by multiple studies and summarized in the most important European or American conferences or guidelines. For example, the 14th St. Gallen International Breast Cancer Conference, 2015 [4], considers breast carcinoma a heterogeneous pathology according to its intrinsic molecular types whereas the 8th edition of AJCC (American Joint Committee on Cancer) states that breast malignant tumours should be staged according to the prognostic group, based on population that had been offered and mostly treated with appropriate endocrine or systemic therapy which includes anatomic T, N and M plus grade and status of HER2, ER, PR. [5]

MATERIAL AND METHOD

The aim of this retrospective analysis was to offer an exhaustive perspective of breast cancer considering clinical and imagistic presentation, morphological and molecular profiles of the main mortality factor for women. We analyzed the breast cancer heterogeneity in 121 cases registered as mastectomies, lumpectomies, quadrantectomies or biopsies in the Pathology Department of the University Emergency Hospital in Bucharest, performed over a period of 1 year (1st January 2017-31st of December 2017). The diagnostic varied from benign lesions (fibroadenoma, fibroadenomatoid mastopathy) to the most common malignancies, NST carcinoma and even rare cases like carcinoma with medullary features, mucinous, adenosquamous, papillary carcinoma or Phyllodes tumor.

Table 1. Frequency of the surgical procedures used for the histopathological diagnoses in the analyzed population

Type of lesion	Mastectomy + axillary in dissection	Lumpectomy	Core needle biopsy	Total
NST	40	19	19	78
NST with papillary features		1		1
Invasive lobular carcinoma	4	1	3	8
Medullary carcinoma	1			1
Adenosquamous carcinoma	1			1
Phyllodes tumour	1			1
Adenomioepithelioma		1		1
Metastasis of B cell lymphoma		1		1
Benign lesions, non-inflammatory	5	5	1	11
Fibroadenomas	1	8	2	11
Benign lesions, inflammatory	1	3		4
Metastasis of breast carcinoma			3	3
Total	54	39	28	121

For clinical data and imagistic interpretation, we used the hospital electronic database. The histologic specimens were studied using both conventional histopathological examination with HE stains and also immunohistochemically methods, classifying them further in the main 4 surrogate-molecular subtypes: luminal A, luminal B, HER2-neu non-luminal and basal-like/triple-negative. For diagnosing the main histologic subtypes, the last WHO guideline criteria were applied. For data collection and processing Microsoft Office Excel 2010 was used.

RESULTS

This one-year retrospective study analyzed 121 cases female patients registered in Pathology Department of the University Emergency Hospital in Bucharest with diagnostic of benign lesions and also with malignant

pathologies. Those included carcinomas, with NST histotype being the most common (78 cases), ILC (8 cases) and also rare types. Detailed information is found in Table 1.

We focused our attention on the most common types of breast carcinoma: NST and ILC. In our study the most common histotype of breast carcinoma was NST, with a predominance of G2 grade of differentiation (59%), followed by an equal percentage of G1 and G3 (8% for each one).

In the absence of precise data about menstrual status, we considering the climax age at 50 years old. With this presumption, most women were postmenopausal (79%), and the average age at presentation was 61.48 years, varying from 35 to 86 years old. Distribution of the analyzed patients according to their age, histotype and molecular profile of their tumor is detailed in Table 2.

Table 2. Age distribution according to the main histotype, grade of differentiation and molecular profile of the most important histotypes of breast carcinoma

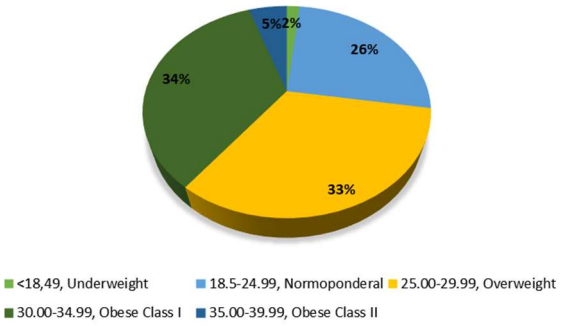
Molecular Profile	Diagnostic					Age					
	0 NST G1	NST G2	NST G3	CLI G2	CLI G3	31-40	41-50	51-60	61-70	71-80	81-90
Luminal A	9%	11%	0%	2%	0%	1%	5%	5%	8%	3%	1%
Luminal B	5%	32%	3%	1%	2%	2%	5%	10%	14%	13%	3%
HER 2 Enriched	0%	3%	1%	0%	0%	0%	1%	0%	1%	2%	0%
Triple Negative Basal Like	0%	6%	5%	0%	0%	0%	1%	1%	7%	2%	0%
Missing Data	1%	9%	0%	3%	0%	1%	3%	1%	6%	2%	0%

Most patients addressed to surgery or Obstetrics-Gynecology Departments of the University Emergency Hospital in Bucharest for painless tumor masses. We also noticed sporadic cases of ulcerated bleeding tumors. A single patient presented for asymptomatic tumor incidental discovered with mammographic screening.

A demographic brief analysis revealed that most patient came from urban areas, with a percentage of 56% for the latter and 44% for rural areas; taking a closer look, we observed that the majority of advanced stages (III and IV) were more frequent in women with urban provenience (10.7% for stage III respective 4.7% for stage IV) in comparison to rural population that addressed to our hospital (1.2% stage III and 0.6% for stage IV).

Regarding clinical data obtained from hospital database, we noticed that the metabolic profile of a majority of analyzed women was impaired, most of them being overweight and obese, only a quarter bearing a normal weight, as the Figure 1 reveals. More than half of studied patients suffered dyslipidemia and experienced cardiovascular complications (essential hypertension and atherosclerosis were most noted). A subgroup also registered a history of gynecologic or endocrine pathology but not enough for a trustable correlation.

Figure 1. BMI of analyzed cases

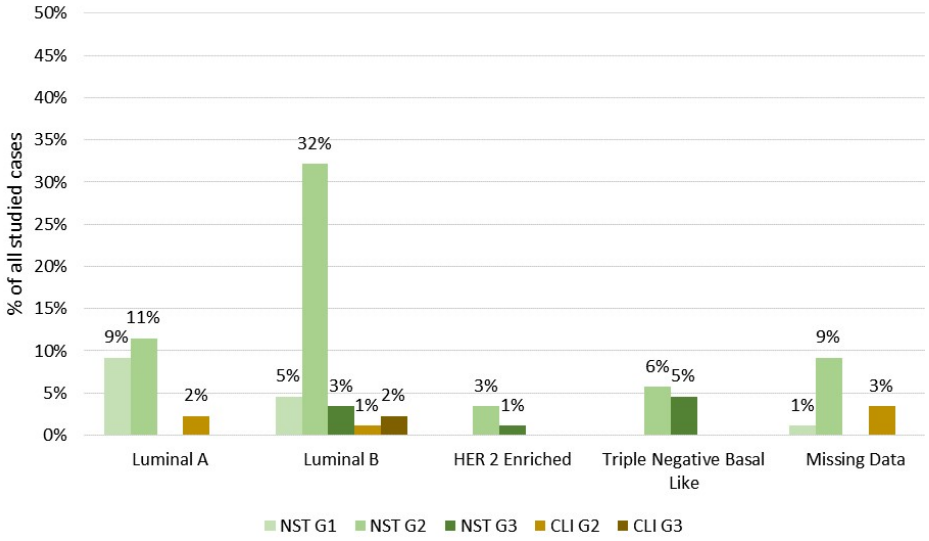


When we put side by side the matric data of different types of investigations (ultrasonography, mammography at CT) with histopathological measurement (macroscopically and microscopically evaluation) we noticed that the highest accuracy in appreciating the dimension of breast lesions is radiologic examination (mammography and CT), followed by ultrasonography which tend to underestimate most of lesions. Considering the main histotypes, the most difficult breast tumor to be precisely measured in conventional imagistic methods is invasive lobular carcinoma, in accordance with its manner of infiltrating the mammary tissue.

With the available data, we observed that invasive breast carcinomas were all scored with BIRADS 5 or 6, a single case of NST G1, luminal A, T1c being

underappreciated as 3.

Figure 2. Molecular profile of breast carcinoma according to histotype (%)



In relation to histologic examination of breast cancer, formalin fixed-paraffin-embedded tissue were studied using both conventional histopathological examination including HE stains and also immunohistochemically methods, classifying them further in the 4 main surrogate-molecular subtypes: luminal A, luminal B, HER2-neu non-luminal and basal-like/triple-negative. For diagnosing the main histologic subtypes, the last WHO guideline criteria were used.

When we evaluated breast cancer histotypes and their molecular pattern, we observed that the most prevalent is luminal B with a pick incidence in NST grade 2, followed by luminal A, also most prevalent for NST G2.

The oncologic stage according to WHO 2014 for HER 2 enriched and triple negative varied between IIB and IV. We did not find any single case in stage I. We also observed that for luminal A category the majority of cancer were in stage I and II. An interesting aspect is registered for luminal B, the most frequent molecular type of our statistic. We can easily observe that it has the highest frequency in most of cases, but not in stage I of disease. A more explicative illustration of the preponderance of tumor stages according to the 7th edition of UICC for TNM classification of malignant tumors, in relation to their molecular profile is highlighted in figure 3.

Figure 3. Molecular profiles of tumor stages related to the molecular profile

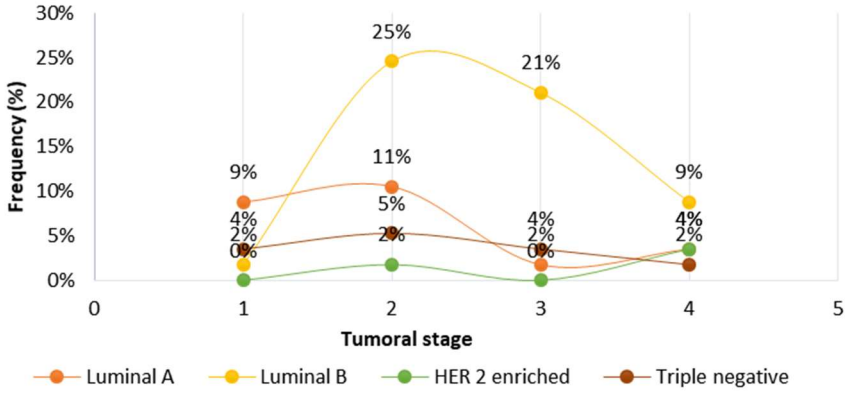
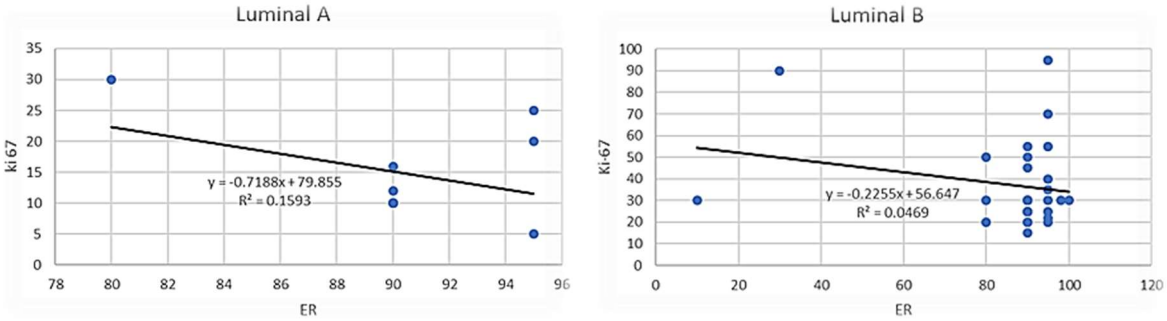


Figure 4. Regression between ER expression and KI 67 in luminal A and luminal B breast carcinomas



Considering the hormonal expression in the luminal type carcinomas and their proliferation index, we observed the regression between ER expression and the mitotic index evaluated by Ki 67 in luminal molecular profiles. For luminal A there is a better correlation between a higher expression of ER and a lower Ki 67 (R2=0.159) comparing to luminal B (R2=0.046), as in the Figure 4 can be easily seen. The juxtapose of the two types was not only useful for understanding the variation of hormonal variation regarding the proliferation rate, but also necessary considering the limited number of analyzed cases.

In our study, no invasive lobular breast carcinoma was identified among non-luminal carcinomas. We registered more triple negative than HER 2 enriched molecular subtype, and their prevalence were highest in climax women. As expected, their histologic features were more aggressive, with large areas of necrosis, infiltrative pattern of growth, and large numbers of mitoses, none of those being graded as well differentiated.

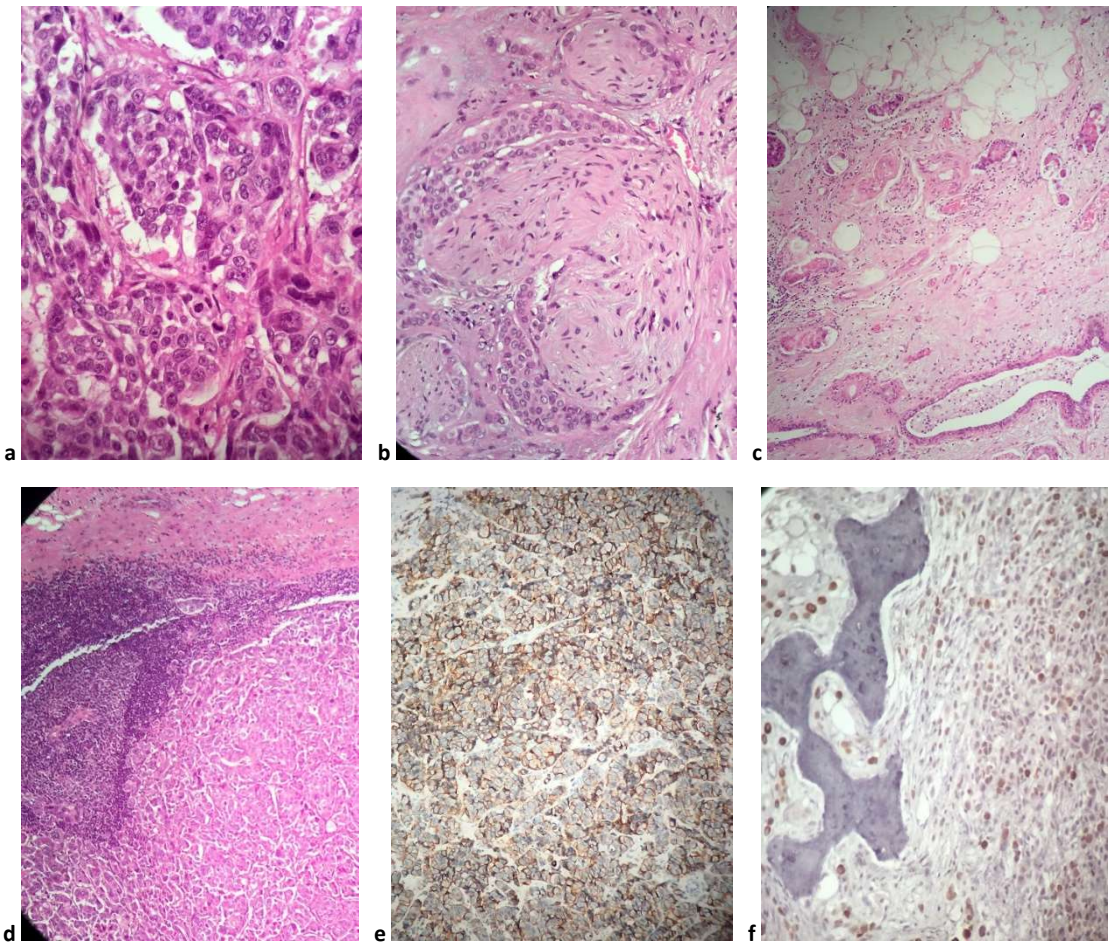
DISCUSSION

Breast carcinoma is not a single disease, it has a large panel of shapes, clinical manifestations, imagistic and histologic representations. The current WHO guidelines for breast carcinoma counts 37 different coded histotypes, but this classification it is far from being adequate for proper treatment [6]. Tumors with identical clinical and pathological presentations may have different behaviors. Beside the TNM classification and grading method (today the Nottingham histologic score system is universally accepted), the interest for treating in the most efficient and precise way each particular biological form of disease gave birth to the molecular subtype classification. This procedure evaluates the hormonal expression of tumor tissue (ER, PR), presence or absence of HER2 protein and levels of Ki-67.

We started our analysis by looking on the preferred diagnostic procedure, and in some cases, it was similar with the surgical treatment. The method of choice for the majority of invasive breast carcinoma clinically diagnosed is represented by mastectomies with axillary lymph node dissections were. Most of these procedures started with a frozen section for certifying the malignant nature of the lesion. After the frozen section, surgical interventions ended with mastectomy and lymph node dissection. Less than half of analyzed women received a neoadjuvant chemo-radio-therapy after core needle biopsy and came back for completing the surgical treatment.

The concordance of core needle biopsy and surgical excision specimen for diagnosing the histotype and hormonal profile of the tumor was proofed to be safe in large studies [7, 8]. According to ESMO, assessment of primary tumor includes: physical examination, mammography, breast ultrasound for lymph node determination, breast MRI and core biopsy with pathology determination of histotype, grade, ER, PR, HER-2 and Ki67 status. If preoperative systemic therapy is planned, a core needle biopsy is mandatory to ensure a diagnosis of invasive disease and assess biomarkers (recommendation IIIA) [9].

Figure 5. NST HER2 enriched carcinoma a. Numerous atypical mitosis HE 40X; b. perineural invasion, HE 40X; c. Intravascular tumor emboli; d. Lymph node invasion, HE 10X; e. HER2 intensely positive, scored 3+, 20X; HER2 negative, score 0, 20X.; f. Bone metastases with GATA 3 positivity suggesting breast origin, 20X.



Since it is not yet a standardized method, CNB does not represent a IA indication for non-operative diagnostic. Even if the Royal College of Pathology [10], the WHO guidelines for breast cancer and AJCC 8th edition [5] enclose certain recommendation for reporting the results of a CNB, this practice is controversial regarding the rate of metastasis [11], the reliability of histological grade considering the dimensions of collected fragments [12], the limitation in diagnosing certain subtypes of carcinoma (e.g. mucinous carcinoma) [13], and even rise the problem of "vanishing carcinoma", when tumor cells are present on CNB but absent in the surgical specimen [14];

We focused our attention on the most frequent histotypes of breast tumors, NST and ILC. The rare types of malignancies like papillary carcinoma, medullary carcinoma, Phyllodes tumor or metastasis to the breast are not well represented in this one-year study and for the sake of statistic relevance, we choose not to include them in our calculation. Also, the benign lesions (fibroadenoma, adenomyoepithelioma, abscesses or fibrocystic disease) were not relevant for the heterogeneity of breast carcinoma.

The interesting demographic results that we obtained underlines that the majority of severe stages of disease (stage III and IV) were addressed from urban population. This trend is not observed in other studies made in Australia [15], Africa [16] or even in multiethnic and multiracial population [17], but in our opinion, these unexpected results may appear because of many reasons: probably the most important one is the limited number of cases that

were included in our analysis. Other reasons may consider the higher addressability of urban women to private health system, the migration of urban population to the country side or a better surveillance of patients from rural area by their family doctor. On a deeper assessment, it is easily noticed that most of our luminal B cases had a high Ki 67 index (above 20%), only a third of them being HER2 positive or equivoque on IHC. A possible explanation could be the absence of a -ISH method in our department for a precise assessment of HER 2 mutation. Anyway, considering the limited period and number of analyzed cases, for a more accurate distribution of luminal subtypes more studies are needed.

Taking into account hormonal expression, using regressions, we observed that for luminal A molecular subtype the higher the estrogen receptor expression is, the lower the proliferation index is (quantified by Ki 67); in comparison, for luminal B subtype p-value was only 0.0469.

Regarding the age, the highest amount of breast cancers appeared in the 6th decade of life, with a considerable delimitation between pre- and post-menopausal age. Even so, in the 3rd decade we registered only luminal subtypes of cancer (considered to have a better prognosis) but in the 4th decade we registered all the molecular subtypes.

Regarding clinical correlation, we became aware of the impaired weight of our studied group, most patients being overweight, with a medium BMI of 27.73. Also, we noticed that a great proportion of studied women who underwent a diagnostic biopsy and returned after approximately 3 months for surgical treatment gained extra kg, their BMI being augmented. This observation could be an alarm signal for a better nutritional surveillance and psychologic management of oncologic patients, considering that obesity it is an important risk factor for malignancy, comorbidities and mortality [18 - 20].

Unfortunately, our clinical correlation was limited because we did not had access to variables like family and history of menstruation, oral contraceptive use, age of first full-term pregnancy, number of children, duration of lactation or hormonal replacement therapy.

CONCLUSIONS

In our study, primary malignant epithelial tumors of the breast were NST with a moderate grade of differentiation with an age of incidence ranging from 3rd to 8th decade, being most prevalent in the 6th decade. Regarding molecular classification, luminal B was more common than others, with a wide clinical and histologic appearance; it was found in all analyzed histotypes and in all pathologic stages of disease. Because of its predominance, most of severe cases we registered (metastatic breast disease, ulcerated tumors) were also luminal B subtype. We admit the limitations of our study (few cases in a single year in a single hospital with emergency profile) but we are convinced that for a better breast cancer management, keeping in mind the most important aim, a lower mortality and morbidity, a proper national screening program is of an imperative necessity.

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SYSTEMATIC REVIEW

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Analysis of risk factors for antipsychotic-resistant schizophrenia in young patients – A retrospective analysis

Octavian Vasiliu[1], Daniel Vasile[1,2], Andreea F. Făinărea[1], Mihaela C. Pătrașcu[1], Elena A. Morariu[1], Raluca Manolache[1], Iulia Alexandru[1], Flavius T. Androne[1]

Abstract: *Treatment resistant schizophrenia (TRS) is a severely disabling disorder, which decreases dramatically the quality of life and overall functionality, while it increases the rate of hospital admissions and overall healthcare costs. The main objective of this research was to evaluate the risk factors for TRS in a group of patients based on a retrospective analysis. The secondary objective was to design an algorithm for initial evaluation in patients with schizophrenia, in order to detect the candidates at risk for developing TRS. Medical charts and consultation records of all patients aged between 18 and 30, diagnosed with TRS, evaluated during 1-year in our department, were selected for analysis. The most significant risk factors for TRS found in univariate model were younger age at schizophrenia onset, male gender, living in rural areas, co-morbid drug dependence, lower therapeutic adherence, and premorbid personality disorder. Marginally significant were higher Positive and Negative Syndrome Scale (PANSS) scores at previous admissions, higher scores on PANSS negative symptoms sub-scale, and lower educational background. In the multivariate model, TRS was still significantly predicted ($p<0.05$) by younger age at the disease onset, addictive co-morbidity, and lower therapeutic adherence. An algorithm based on these risk factors is suggested, based on (a) structured PANSS evaluation using SCI-PANSS and Informant Questionnaire for PANSS, (b) a scale for the detection of co-morbid drug dependence (i.e. Inventory of Drug Taking Situations, IDTS), (c) an interview for detecting premorbid personality disorders (i.e. Structured Clinical Interview for DSM IV – Axis II Disorders, SCID-II), and (d) Treatment Satisfaction Questionnaire for Medication (TSQM) for therapeutic adherence monitoring. Also, the inclusion of several pharmacogenetic parameters (at least CYP450 2D6 panel for detection of poor/ultrarapid metabolizers) could be useful when establishing an adequate therapeutic management, and may help in decreasing the rate of non-response due to variations in antipsychotics plasma levels.*

Keywords: *antipsychotics, treatment-resistant schizophrenia, pharmacogenetics, therapeutic adherence, co-morbidity*

TREATMENT-RESISTANT SCHIZOPHRENIA IN YOUNG PATIENTS – CURRENT STAGE OF RESEARCH

Young age is an important negative prognosis factor in patients diagnosed with schizophrenia, and individuals aged 26 or less at their first psychotic episode have a higher risk to be treatment-resistant [1]. This phenomenon has significant impact over patients and their caregivers functionality, but also involves higher costs for society, and especially for the healthcare system.

[1] Carol Davila University Emergency Central Military Hospital, Bucharest

[2] Carol Davila University of Medicine and Pharmacy, Faculty of Medicine, Bucharest

Treatment resistant schizophrenia (TRS) is defined by the lack of significant clinical improvement despite therapy with two different antipsychotics from at least two different chemical classes (at least one is an atypical agent) in the previous 5 years at recommended doses for at least 2-8 weeks each drug [2]. Other definitions are more inclusive, stating that resistance is observed when the patient has inadequate response to at least two antipsychotic drugs at the maximally tolerated dose within the recommended therapeutic range in trials of at least 6 weeks [3].

Pseudo-resistance may be attributed to a large spectrum of factors, i.e. lack of therapeutic adherence, co-morbid psychiatric and/or somatic disorders, pharmacokinetic interactions, and pharmacodynamic negative impact of concomitant medication. Also, from a pragmatic perspective, cases of partial response or lack of response may be related to changes of generic antipsychotics, i.e. in patients who take different products (although with the same non-proprietary names) during successive months, due to economic or administrative issues. This observation is supported by at least a literature review which confirms clinical deterioration, adverse effects, and changes in pharmacokinetics associated with generic substitution of several psychotropics, antipsychotics included, while generics do not always lead to anticipated monetary savings and raise compliance issues [4].

To make things more complicated, certain pharmacological strategies could produce ambiguous results, i.e. combining two or more antipsychotic agents is a practice observed in more than 40% of patients with schizophrenia [5]. It's very difficult in these cases to differentiate the effect of each drug, and to monitor the clinical evolution of such patients.

A re-evaluation of the diagnosis is granted in all cases of non-response, and various psychological factors that could worsen the patient's overall status should be addressed by the case manager (i.e. housing instability or homelessness, lack of integration in the medical health system, familial conflicts). Integration of these factors in the therapeutic management of schizophrenia as possible factors for decreasing the response rate should be considered good practice.

Currently it is assumed that one third of the patients who has schizophrenia don't respond to an adequate treatment [6]. Even if these patients are switched on clozapine, after two failed trials with different antipsychotics, up to 40% of them will experience only partial remission, and full functional recovery is impossible for more than half of these individuals [7].

Various predictors for poor treatment response were reported, i.e. severity of negative symptoms, or low level of premorbid functioning [8]. Treatment-resistant patients present glutamatergic abnormalities, a lack of dopaminergic abnormalities, higher familial loading, and significant decrease in grey matter compared to responsive patients, which raises the question if a distinct type of schizophrenia could be detected from the very beggining [8]. An analysis of adult patients with TRS (N=8624) included in the Danish National Registry showed that higher rates of treatment-resistance were observed in younger individuals, living in rural or provincial areas, with lower education level, hospitalised over 30 days in the year before first schizophrenia diagnosis, who were in-patients at first schizophrenia diagnosis, with paranoid subtype, comorbid personality disorder, and/or previous suicide attempt, who used multiple psychotropic drugs (antipsychotics, antidepressants, or benzodiazepines) [9].

Pharmacogenetic studies detected associations between genes polymorphisms in pharmacokinetic (i.e. cytochrome P450 1A2 and 2D6 isoenzymes) and pharmacodynamic (i.e. D2, D4, and 5HT2A receptors) factors, and response to antipsychotics [10]. These genes are involved in various stages of processing and action of antipsychotics, from the hepatic metabolism to generation of various adverse events. If all these factors could be defined on large-scale trials, they could improve the efficacy and tolerability of antipsychotic treatment, in a future personalised medicine. Until then, several studies and case reports linked functionally 5HT3 receptors gene single-nucleotide polymorphisms (SNP) to the clozapine responsivity, and CYP1A2*1F genetic polymorphism to the clozapine metabolism [11,12]. Both these observations could explain several cases of TRS, but

larger trials are needed to confirm these reports.

A predictive model for therapeutic response in schizophrenia, based on logistic regression analyses, was suggested, and it showed that 76% of the patients carrying combination of four SNPs will have a lower response to atypical antipsychotic monotherapy [13].

Another interesting suggestion is classifying schizophrenia in different subtypes, based on biological markers, clinical staging (illness severity, prognosis, and therapeutic options), and treatment response [14]. Antipsychotic responsive schizophrenia, clozapine responsive schizophrenia, and clozapine resistant schizophrenia are the subtypes suggested by this model [14]. This classification may have important prognostic value and could help clinicians in formulating an adequate therapeutic management. Unfortunately, no good quality data exist for the next step in the treatment of clozapine-resistant patients, although co-prescribing a second atypical antipsychotic, a selective serotonin reuptake inhibitor, lithium or divalproex, glycine or D-cycloserine, and memantine has been investigated with low to moderate success [15].

Table 1. Demographic and disorder-related variables at the evaluation visit

Variables	Values	Observations
Current age	26.1 (range 18-30)	Only young patients were included in the analysis
Age at onset of the disorder	22.9 (range 18-29)	
Gender *Female* *Male*	 8 7	 53.3% 46.7%
Environment *Rural* *Urban*	 7 8	 46.7% 53.3%
Marital status *Single (including unmarried and divorced)* *Married*	 11 4	 73.3% 26.7%
Social status/income *High* *Medium* *Low*	 1 4 10	 6.7% 26.7% 66.6%
Independent living Institutionalized	14 1	This proportion could be due to the addressability of our department
Number of previous psychotic episodes	0.6 (range 0-3)	Most of the patients were at their second psychotic episode
Substance related disorders present (nicotine dependence included)	11	9%
Personality disorders present	8	53.3%
PANSS overall score PANSS-negative Scale PANSS-positive Scale	91.8 (range 86-122) 30.5 (range 15-40) 32.6 (range 20-42)	
Length of the current episode (weeks)	12.5 (range 6-30)	

OBJECTIVE AND METHODS

The main objective of this research was to evaluate the risk factors for TRS in a group of patients based on a retrospective analysis.

The secondary objective was to design an algorithm for initial evaluation in patients with schizophrenia, in order to detect the candidates at risk for developing TRS.

Medical charts and consultation records of all patients aged between 18 and 30, diagnosed with TRS,

evaluated during 1-year in our department, were selected for analysis. A number of 15 TRS cases were detected from a total of 68 patients diagnosed with schizophrenia. The diagnosis of TRS was based on DSM IV TR criteria and the World Federation of Societies of Biological Psychiatry Guidelines for Schizophrenia criteria [2].

A logistic regression analysis using SPSS 22.0 was performed on 25 demographic, clinical, and therapeutic variables, in a univariate, followed by a multivariate model. No pharmacogenetic variables could be identified in the selected medical documents.

RESULTS

The most significant risk factors for TRS in univariate model were younger onset age ($p<0.01$), male gender ($p<0.01$), living in rural areas ($p<0.05$), co-morbid drug dependence ($p<0.05$), lower therapeutic adherence ($p<0.05$), and premorbid personality disorder ($p<0.05$).

Marginally significant in the same univariate model were higher Positive and Negative Syndrome Scale (PANSS) score at previous admissions ($p=0.056$), higher score on PANSS negative symptoms scale ($p=0.058$), and lower educational background ($p=0.061$).

In the multivariate model, TRS was still significantly predicted ($p<0.05$) by younger age at onset ($p=0.022$), addictive co-morbidity ($p=0.042$), and lower therapeutic adherence ($p=0.048$).

Table 2. Risk factors for TRS in young adults

Factors	Values	
	Spearman's ρ	Linear regression p
Younger age at the current episode onset	0.467	<0.01
Gender – male	0.592	<0.01
Substance-related disorder comorbidity	0.320	<0.05
Living in rural areas	0.367	<0.05
Lower therapeutic adherence	0.322	<0.05
Premorbid personality disorder	0.298	<0.05
PANSS overall score at previous admission	0.155	0.056
PANSS-Negative Scale current score	0.152	0.058
Lower educational background	0.142	0.061

An algorithm based on these risk factors is suggested, based on:

(a) Structured PANSS evaluation based on SCI-PANSS and Informant Questionnaire for PANSS, because the previous PANSS overall scores and current Negative Scale score are correlated with the patients risk for developing TRS;

(b) A scale for the detection of co-morbid drug dependence (i.e. Inventory of Drug Taking Situations, IDTS), because current drug-related disorders should be integrated in the therapeutic management, and it has prognostic value;

(c) An interview for detecting premorbid personality disorders (i.e. Structured Clinical Interview for DSM IV – Axis II Disorders, SCID-II), because of the correlation between the risk for TRS and several premorbid disorders (especially cluster A disorders);

(d) Treatment Satisfaction Questionnaire for Medication (TSQM) for the monitorisation of therapeutic adherence, because a low therapeutic adherence is a major risk factor for developing treatment-resistance

Also, the inclusion of several pharmacogenetic parameters (at least CYP450 2D6 panel for detection of poor/ultrafast metabolizers) could be useful when establishing an adequate therapeutic management, and may help in decreasing the rate of non-response due to variations in antipsychotics plasma levels. This could have important pharmacoeconomic impact, since many antipsychotics undergo hepatic

metabolism, not to mention the risk of potential pharmacokinetic interactions between antipsychotics, or between antipsychotics and other co-administered drugs.

CONCLUSIONS

Analysis of risk factors for TRS should be included in an evaluation algorithm for all patients diagnosed with schizophrenia. While some risk factors could not be influenced therapeutically, still others can be addressed, with targeted intervention for co-morbid addictive disorders, personality disorders, negative symptoms, or with techniques for increasing therapeutic adherence.

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Blending between occultism and scientism in Vasile Voiculescu's short stories

Mirela Radu[1]

Abstract: *Vasile Voiculescu (1884-1963), besides being a well-known writer, was also a prominent, much respected physician who practiced between the two world wars. He attended the courses of the Faculty of Letters and Philosophy in Bucharest for a year (1902-1903), but gave up on them in order to attend the Faculty of Medicine. The literary debut took place in 1912 in the journal Convorbiri literare. He published the first volume of lyrical poems in 1916 and in 1918 he was granted the Academy Award for lyrical volume From the Aurochs Country and other poems. In 1935 he became a member of the Academy of Sciences of Romania and in 1941 he received the National Poetry Prize. The following volumes of poems are: Ripeness (1921), Poems with Angels (1927), Destiny (1933), Ascent (1937), Gleams (1939). His work also includes a short story: The Demiurge (1943). Shakespeare's last imaginative sonnets in Vasile Voiculescu's translation (1964), and the novel Zahei-The blind (1966), Sentimental Gymnastics (1972) are published posthumously. The present article is aimed at revealing the world of Voiculescu's short stories.*

Keywords: *medical studies, abyssal psychology, scientism, mystery, obscurity*

[1] Titu Maiorescu University, Faculty of Medicine, Bucharest

Although the most analyzed part of Voiculescu's work seems to be his poetry, he proved his worth in the same manner in storytelling. His creative enthusiasm needed several means of expression as Voiculescu the poet was sometimes haunted by a "spirit of storytelling manifested as a spontaneous eruption." [1]

His inspiration manifested itself as prose also because creative adaptability seems to grow with age: "As the man seemed to «bend under the weight of the years», the creator received new powers, as a sum of his life's and artistic experience by a high level of expression, in a veritable eruption if poetry, in verses and prose." [2] The surprise comes from the chameleonic nature of the author who took on prose with different motives than those in his poetry, coming out as a writer who was: "(…) a perfect master of his own means, not related in any way with the poet." [3] Voiculescu's stories are that much more appealing as they give the sensation of combining some fantasies from the folkloric supernatural, amusing stories, hunting adventures but also "(…) oddities to be told at midnight, parapsychological medical cases etc., which the author attributes a narrative density, emphasizes their equivoque and gives them a superior meaning through the means of literature." [4]

What characterizes the doctrinal physicist's stories are miraculous happenings populated by divine characters

with an occult composition, "(...) in which «the efficiency of symbols» is not alien to the writer's anthropomorphic manner." [5] Some of his stories seek to demystify believes: the conviction that the shadow building can lead to death (The shadow, 1935), even to the actualization of some pseudo-scientific procedures of rejuvenation fashionable at the time, among which the method of doctor Sergiu Voronoff for grafting of some glands called by him interstitial, a method that was widely debated in the periodicals of the time [6] (The Demiurge, 1943) [7]. The connection between certain life forms represents the main theme in the physician's novellas. The influence of medical studies is present due to the fact that Voiculescu combines the folkloric preconceptions with scientific revelations and with: "the hypothesis and conclusions of modern experimental psychology (…). [8] The reason for his leaning towards folkloric heresies was the fact that, being in a permanent search for answers, the literate-physician did find them even in practiced medicine. Unlike other prose writers with folkloric roots, Voiculescu's characters are fantastic with occult origins. Some critics noticed his short stories astonishing capability of entwining the new with the old, and of "discovering pathways of the archaic in the modern, some depths of existence itself, this causing Voiculescu to write some of his best prose." [9]

Supernatural, mystery and obscurity were what fascinated him, ticking his interest even before his medical studies in :"(…) heresies, magical symbols, in one word the occult part of existence." [10] Unavoidably, the permanent dispute in his soul between objectivity and belief can be seen in his work. A proof in this this sense is represented but the fact that in his short stories, the author uses characters that, if not belonging to the medical world, at least belong to the scientific one, meant to shed an accessible perspective of fantastic events to the reader. These characters can be considered an alter-ego of the author, his nature of undressing every fantastic element by finding a clear explanation, or are either introduced in order for the reader to decipher the message. In a world in which the occult loses ground to the prosaic, these characters anchored in the real world have the task of opening doors through which a new reality can be either seen or understood.

The separation of social and personal life is impossible. This can be seen in Voiculescu's work. The contaminations from one to another: living scientifically but sensing aesthetically can be found in written pieces: "(…) the diagnostician and the therapist can be found, in way or another in writing (…) but the physician-writer relationship can reside in other places too and can be the subject of a study on man, as a professional in medicine but also in prose, who borrows aspects of the life and work of the former." [11] This combination can only occur by presenting bizarre medical cases, almost always pathological.

To prove this deduction, Florentin Popescu brings the example of the short story The cursed cow (written by the literate-physician in only one day, 27th February 1947) which portraits the morbid case of zoophilia between a spoon maker who satisfies his sexual urges with the cow, Dumana. The short story Dead season (2nd June 1948) from the volume Magical love appeals to psycho-analysis. This time, the character dominated by rationalism- physician Charles and his dog Azor are preyed upon by a mysterious force. Azor mates with a fox and the medic with a peasant. Everything comes back to normal when the mystical element, the fox, is slain. The explanation that the rational man-Charles-tries to attribute to the semi-hypnotic event is insolation and the effect that the moon had on him: "Meaning that his brain was struck by the too powerful light of the moon. Like others get insolation, there are some more sensible to the magnetic waves of the moon." [12] Some exegetes saw this piece as a case of "ecological Freudiansim" [13], a way of setting loose the sexual restraints. The same as in other stories of Voiculescu, the deeds are described by a narrator which seeks to be objective, doctor X, "… medic and poet in his free time." [14] This same narrator has he role of arguer, even if he doesn't acknowledge his ability to psycho-analyze the events "I am not a psychologist and less a Freudian (…) I never sought an explanation for humanism that erupted in him covering the self-imposed artificially to himself." [15] The writer does not judge, and nor does he incline the scale towards cabalistic or rationalism, he just offers

facts left for the reader to judge and decipher. "His interest goes towards a magical underlay in the peasant's spirituality, which he does not judge or condemn." [16]

Dramaturgy represents another aspect under which the inner torments of the Voiculescu, the physician-literate, developed on paper. Among his plays are The wanderer, Sentimental Gymnastics and The Demiurge. In Sentimental Gymnastics, a commoner, Ion Ionescu, comes in touch with psychological elements from William James' doctrine when he receives training, from an ex-colleague – Puiu Moldovian, in repressing affective emotions. The purpose of this training is that of freeing the character from doubts and boosting his self-esteem. If professionally this turn of events is favorable to him, sentimentally it ends in a failure as he becomes too attractive to the women in his town who will fall prey to his charm.

The influence of Expressionism can be seen in the short story On the miracle doorstep (1934) also named dramatic poem in which the issues of religion and fantasy are exposed. Itic Holzfleisch carries the burden of introducing a new religion to mankind. Because of his lack of credibility he is arrested. In prison he hangs himself behind the door where passers could not see him. Because of his supposed disappearance Itic is thought to indeed possess supernatural powers and can become invisible. The miracle though is not fully completed, hence the key in the title – "on the doorstep" – meaning on the edge. Ovid. S. Crohmălniceanu identifies a Verkundigung Drama in this short story. By not respecting any canons, this short story presents itself as an "authentic modern «mystery»." [17] Religious in appearance, the short story could be labeled in the template set by Gândirea, but by shedding light on the main character's inner feelings, the critic perceives it as expressionistic. The same Ovid. S. Crohmălniceanu considers another two short stories belonging to the same literary current, The shadow and The bear's girl, both published in 1930 and then included in 1943 into The Earth's spirit.

The short story The Demiurge (1943) precedes the nightmare that Europe would live three years later: the second worldwide conflagration and the Nazis' experiments for perfecting the pure race. This time, the main character is yet again a medic: Muşatin. Descendant of an old family he seeks to refresh his family's genealogy by gene amelioration. In order to do this, he focuses on experiments, at first on animals, and later on human beings. Lucian, his son, does not agree with his father's conceptions and becomes his victim, having his passion and sexual characteristics removed. The critics saw this short story not only as a S.F. one, but also as a mockery, from a scientific standpoint, of certain theories that would later become a nightmare, thus providing: "a virulent and convincing satire on the dangerous fascist theory of race amelioration and dramatically-beyond value, resistance in the face of critics and posterity- probes the lucid, realistic and healthy position of a physician in the face of some aberration which humanity has lived at a certain time in history." [18]

To narrow down The Demiurge to either the categorization of a satire or a S.F. short story is a narrow angle of analysis. The short story represents a new phase for the political drama. The utilization of science to the damage of mankind and the certainty that a scientist can replace God make this short story an outpost of Romanian novellas with political connotations, resembling with "The physicists by Durenmatt" [19] in its intrigue. Just like Faust, Muşatin defies morality, makes a pact in which his own son will fall: the physician transplants his son's genital organs to an elderly person. Other critics claimed to Romanticism the doctor's ability to fuse the real with the fantastic, by embracing revelry and creation. Belonging also to Romanticism is his approach on national history, as an"(…) altar on which he issued canonicals." [20]

Voiculescu's characters take on magical properties, through spells and calling upon magic being able to access a world separated from the perceivable knowledge. This can be seen in the short story In the middle of the wolves (written 2nd May 1947). This time the reasoning main character is a magistrate that collects folkloric elements. To his astonishment, people around him think greatly of him because of his belief of having supernatural powers. The character meets Lupar, the one that used wolves instead of dogs. The influence of the studies attended by the author

can be seen in the characterization of Lupar, which resembles the physiognomy of the criminal noted by Cesare Lombroso, Italian physician and criminalist. In order to get closer to this bizarre character, the magistrate admits that he is no stranger to magical practices, as he practiced spiritism. The physician-literate, as Eugen Simion also noted, has the ability to reiterate mythical elements, through refinement, he refreshes them without fatiguing the reader: "V. Voiculescu uses folkloric syncretism which grants him the ability to update the myths without seeming outdated or suggesting their social death and without sociologism and ethnography." [21]

If it is natural to appreciate the pages which send you towards the abyssal psychology thanks to the knowledge Voiculescu gained in his years of medical study, other critics see those writing that forego scientism and appeal to the fabulous as having a real value: "The storyteller Voiculescu finds his own space in those stories in which he steps in not as a psychologist or a social-moralist but as a character in contingency with the unnatural and supernatural." [22] These short stories filled up with an electrifying combination of the profane and sacred, a world which the prose writer does not reveal to the reader but rather lets him discover it, make the author a homo religious. [23]

This effort to reveal the intangible needs to be appreciated even more so knowing that behind the author hides a rational nature, a man of science dominated by practicality and who values systems of rational thinking and deductive judgment: "The positivism of the physician and the rationalism as the love of beings and things of the spiritual man impregnated Voiculescu's stories with the resin that makes objects durable, giving them good clerical fragrance." [24]

Originating from an urban environment, the characters from Voiculescu's short stories are townsfolk which fight a battle of regaining the right to dream, opposing the civilized world which estranges them from their fabulous origins, as the society from which they originate alienates the human being "through the abolishing of humanity." [25] These urbanites fall prey to devouring love, as humanly as possible, and the magic is given off by "beings with a htonic power." [26] Voiculescu remodels reality enriching the means of sensible knowledge: "Sooner a systematic try of apprehending reality through abundancy of sensations, though the equity of perception." [27] As any men of science, Voiculescu is inclined towards explaining in a somewhat scientific manner, in a rational way all deeds that appear irrational." [28] And these explanations are given through the prism of psychoanalysis and psychology.

Treated by some critics as epigrammatic dystopia, Prefrontal Lobo coagulation appears in 1948, meant as a caustic response, a counterweight to the work of the American psychiatrist Benjamin Karpman, entitled Prefrontal Lobes, enemies of humanity. The work references a practice which would end up serving communism through the psychiatric reprogramming of individuals, of creating "new" people and through eugenics. Voiculescu's short story has the merit of constructing itself in a "revelatory text specifically for Voiculescu's harsh perspective and for the pioneering that is represented by his work." [29] Written on the 27th of July 1948, the short story will be printed only later in the journal Transylvania, in its 9th number of the year 1966. Another source of the short story is found in an article signed by Pierre Wertheimer published on the 10th of July 1948 in the French periodical Medical Presses. Voiculescu's short story is not just a S.F. story, even though many a people identified it as such, but also a ridicule of such deviant practices which were used by the Nazi as well.

The new social order is imposed by the Perfect Permanent Presidium of the Nations for Peace and the newborns are subject to an operations that have as a goal the removal of the prefrontal cerebral lobes, whose physiological function is the adjustment of personality. Initially, this intervention has as subjects, those who belong to certain classes, such as: "the sick, anxious, melancholic, suicidal, perfectionists, schizophrenics, mad men, which often times brought them back to normal." [30] The goal was that of neutralizing possible revolutionary elements though the "affective sterilization, aiming especially for the nervous centers of unrest and revolt." For a bigger impact the medic Voiculescu goes through with the

description of the inhuman procedure: “But then it was a barbaric procedure. The medic would make two holes in the cranium and then search blindly and cut the roots of the required fibers.” [31] Later they would resort to a less invasive method, automated radio coagulation, which is applied to all people, striving for the numbing of emotions.

To the stupor of all scientists who saw the operation as the perfect way of relieving people from sentiments and emotions, the youth would first present physiological secondary effects such as: “dyspepsia, problems with digestion, lack of appetite, anemia, and especially constipation” followed by reactions that danger the procedure itself: “the disorders took a psychological turn among the youth, the cases of soul sufferings started to stain the once impeccable epithelium of the P.P.P.P.P and the wanderings started to multiply.” [32] People become more and more independent and are surprised by waves of feelings, daring to feel and even love.

The danger proved way greater: people try to be conscious of spirit. Although these manifestations of revolt are harshly punished, scientists try to answer the question if: “not somehow those blasted fibers had awakened some other hidden branch, untouched by the coagulator?” The answer seems to be found in the pineal gland, responsible for sexual impulses and as such it is the next organ which will be annihilated through radio coagulation. In vain, as people continue to be affected by affection among which “dreaming, sloth, glittered with names such as meditation, thinking, the work of inner searching, the inclination toward sadness, jealousy, the fight against competitors for a woman, for a job, all kinds of shortcomings, and most of all the fear for the future, all the metaphysical fears, and the sentimental complications took all kinds of shapes, as never seen before” [33] The search for the source of evil continues and end on the conclusion that the hearth modifies itself physically obtaining a new cerebelous structure because:” (...) it changed not only its aspect, form and weight, but also its histological architecture. It was heavier, redder, more globulous, less muscular, and full of nervous fibers and autonomous ganglions” and more striking is the fact that “in the upper part, on its globe, underneath the exit of the aorta, there were some curly buds that resembled brain buds.” [34] Voiculescu ends his story in a more optimistic way and once again proves the power of his medical studies even in building good quality literature.

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Research for the development of logistics planning information support in health protection against biological agents

Lucia E. Ionescu[1], Viorel Ordeanu[1,2], Manuel Dogaru[3], Marius Necșulescu[1], Diana M. Popescu[1], Simona N. Bicheru[1], Gabriela V. Dumitrescu[1]

Abstract: *Making medical countermeasures requires documentation to assess vulnerabilities, threats and operational risks and bioterrorism through the collection and processing of specific multidisciplinary data in human medicine, veterinary, phytosanitary, the environment, defense and national security, etc. Based on retrospective data and late information (medical intelligence), we can estimate the prospective risk to public health, respectively for troops and civilian population in a given area, the area of operations.*

The biological military or bioterrorist attack, whether overtly or masqueraded as human or animal epidemics can cause a major biological crisis for troops and the civilian population, for domestic and wild animals, for crops or wild plants or for the environment, which remains contaminated.

Therefore, it is important to constantly monitor the situation of infectious diseases in the area of responsibility (national territory, operations theaters) to assess vulnerability, threat and bioterrorist risk but also for making medical anti-bioterrorist countermeasures, which can only be effective by genuine cooperation between all specialized structures of the Ministry of Defense, other departments and the civil society.

Keywords: *biological attack, bioterrorism, medical countermeasures, logistics support, medical treatment*

[1] Military Medical Research Center, Bucharest

[2] Titu Maiorescu University, Bucharest

[3] Center for War Games and Doctrinal Experiments CJRED/ S.M.G - former UNAp/ CISM)

INTRODUCTION

Medical protection logistics planning against biological warfare agents (ABR) is based on interdisciplinary studies and specific calculations.

The complexity of this approach involves processing a database of medical, pharmaceutical and logistics that can only be operated in real time by using a suitable IT support. It consists in hardware (IBM compatible standard configuration computer), software (Windows based NATO specific program), specialized personnel (NATO computer operators, specialists in military medicine, logistics, CBRN defense, etc.) and properly equipped and secure space.

Scenarios that simulate hypothetical situations reported in the territory, will be tested by constructive simulation as functional experimental models of "war games ".[1]

EXPERIMENTAL MODELS

Making the experimental model of the information system for constructive simulation for medical protection against biological weapons and bio-terrorism and testing it as a military medical exercise demonstrated and validated the scientific data, using modeling and constructive simulation, together with UNAp/CISM, the current Center for War Games and doctrinal Experiments (CJRED) of the General Staff. [2] It was awarded a large database that can be exploited in different complementary approaches. Of all bacteria, Bacillus anthracis has been chosen for being used in the constructive simulation experiment, it is known as the biologically bacterial agent most used for biological attacks. [3]

Medical countermeasures must be known and individualized for each situation and appropriately applied, with appropriate forces and means. This requires an adequate and efficient logistic support because the scale of medical needs (medicines, sanitary materials, reagents, accommodation, transport, etc.) exponentially increases during an epidemic. As a result, at any level, health-pharmaceutical materials are rapidly becoming inadequate. The unintended consequence is that we cannot prevent illnesses or treat patients, so the affected communities are no longer capable of fighting and working and there is a risk of over mortality. Therefore, the medical protection against biological weapons requires a proper logistic planning that is also based on statistical analysis of some relevant information for this purpose. The exploitation of such data requires a dedicated computer system, with suitable software, trained personnel, quick and secure media and communications, etc. Because the computer system for the surveillance of infectious diseases caused by combat biological agents and by bioterrorism to be reliable, it must be implemented in stages, with feedback in the form of custom scenarios for biological attack or epidemic outbreak.

Achieving this pilot experiment in the Romanian Army, demonstrated the usefulness of extending simulation tests on other categories of warfare and on specific logistics for biological crisis. The system used was JCATS – Joint Conflict and Tactical Simulation. The information was delivered in the form of screen-shots that required image processing, computer analysis and interpretation. [5]

The data was processed and a computer media has been made for logistics planning of medical protection against biological warfare and bioterrorism agents through statistical analysis of the resulting data bank. To estimate the number of contaminants analysis were carried out on the three simulated hypothesis: without sensors, with military sensors and alarm on short (in barracks) and with military sensors and alarm on short distance (in barracks) together with a sensors system of the local Inspectorate for Emergency Situations (ISU) and alarm in the city. We have obtained information that was collated for each simulation, in numerical tables and graphs illustrating the impact such an undesirable event can have. [6]

The obtained data allowed the dynamic evaluation (an estimate every 5 minutes) on the effects of a biological attack with anthrax on cities with different number of inhabitants and military forces.

The post exercise analysis showed that in terms of exposed population, where a relatively small number of people, the presence of the sensor is useful, the number of people being affected (civilian and military) decreased after they triggered the alarm.

In a similar situation, in the case of larger cities it has been observed that activation of military sensors does not cause diminishing the number of affected civilians, but decreases the number of infected soldiers.

The comparative analysis of the post-biological attack, for the soldiers of the sea shows that there are a huge number of people affected in the absence of any alarm sensor (over 50%) as their protection or travel ability is restricted to the soldiers on land. Also, the percentage of affected soldiers who do not benefit from the ship protection is higher (70%), if they go out on the deck.

The major differences recorded between the high percentage of affected civilians and that of the military, leading to the idea that it is useful and necessary for the civilian population to be at least

more informed about how they should act when triggering an alarm of any kind. [7]

Following statistical analysis of the database resulting from constructive simulation system experimentation resulted in an acquisition, storage, retrieval and information-processing algorithm as an interactive database. [8]

SANITARY LOGISTICS

The statistical analysis conduct to information somehow surprising by the extremely high number of people affected, at least from the civilian population, which is not trained to respond to any alarm. Regarding the military, which is a segment of the relatively "trained" population compared to civilians, we found that the number of those affected drastically decreases, especially when special sensors for detection exist. The analysis of relevant simulation for the purpose of the experiment showed that a possible attack with anthrax spores, even if it is not repeatable, it could result in a significant number of contaminated, many of which will develop the disease, and some will die. The evolution of the epidemic will depend on the capacity of the health system (military and civilian) to promptly and adequately act with the necessary forces and means and with the appropriate logistic support, depending on the epidemiological situation of the troops and the civilian population. [8]

This means that all exposed persons should be medically supervised: rapid laboratory analyzes for different areas/neighborhoods, nasal/throat exuding for identifying B. anthracis.

The contaminated must be prophylactic treated, also with antibiotics according to the therapeutic scheme Guide for 60 days and under medical supervision. Patients should be isolated and treated for 60 days. For those with severe forms (pulmonary anthrax) intensive oxygen therapy must be also applied, etc. [9, 10, 11]

The deceased must be disinfected and handed over to and Funeral Services (the civilians) or the Logistics department (military) for transport and burial, in accordance with epidemic provisions. Incineration is contraindicated due to the large number of corpses. Repatriation is not allowed because of the contagion risk. [12]

Overall, the medical forces and means are overburdened and there is an urgent need for specific additional procurement for a 7 week period.

For such need, specific measures are necessary because sanitary-pharmaceutical materials are rapidly becoming inadequate and the only way to overcome the situation involves cooperation with all own and allied military forces as well as civil-military cooperation (CIMIC).

CONCLUSION

- Medical countermeasures against biological or bioterrorist attack are complex and require specialized forces and means, in very large quantities and in real time.
- By medical intelligence the real situation must be known and the short, medium and long term development must be assessed in order to correctly estimate the forces and means necessary for the medical countermeasures.
- By appropriate application of the logistics assurance principles and CIMIC cooperation the specific logistical support can be achieved, necessary to carry out the medical countermeasures for the prevention of diseases and treating patients.
- The logistical support for medical countermeasures against biological or bioterrorist attack must be coherent, efficient and fast.

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Modern methods to differentiate benign thyroid nodules from malignant ones

L. Eftimie[1,2,3], R. Hristu[2], M. Dumitrescu[1], M. Costache[3], S.G. Stanciu[2], M. Sajin[3], G.A. Stanciu[2]

Abstract: *Objective: The purpose of this study is to compare the capsular structure appearing in follicular adenoma and papillary thyroid carcinoma to differentiate the benign and malignant thyroid nodules.*
Methods: Second Harmonic Generation (SHG) Microscopy was used to image collagen distribution in the capsules of several types of nodules. The tissue fragments were formalin-fixed, paraffin-embedded but without H&E staining, with 4-5 microns thick sections. From the same sample, two consecutive sections were made. The first was colored with H&E and capsule images were acquired with an optical microscope. The second was not colored with H&E. On the uncolored sample, type I collagen from the capsule was visualized by SHG microscopy. In addition, a parameter was used to study the orientation of collagen fibers, obtained from the Fast Fourier Transform (FFT) analysis of 2D-images.
Results: SHG microscopy images were acquired to assess the collagen organization of tumoral capsular thyroid nodules previously diagnosed as benign or malignant by conventional H&E staining. Different degree of collagen fibers orientation was observed from the two kinds of capsules and quantified using FFT analysis.
Conclusion: These above described microscopy method can be used to distinguish between benign and malignant thyroid nodules, based on different degree of the capsular collagen fibers orientation.

Keywords*: follicular adenoma, papillary thyroid carcinoma, benign and malignant thyroid nodules, capsular collagen fibers*

[1] Department of Pathology, Central Military Emergency University Hospital "Dr. Carol Davila", Bucharest
[2] Center for Microscopy-Microanalysis and Information Processing, University "Politehnica" of Bucharest, Romania
[3] Department of Pathology - University of Medicine "Carol Davila" Bucharest

INTRODUCTION

The clinical and imagistic diagnosis of malignancy must be confirmed in pathology departments.

Although histopathology and cytopathology are the main tools for diagnosing cancer, there are some difficult cases that pathologists may encounter during routine diagnosis procedures, where the differentiation between a benign tumor proliferations from a malignant one is very difficult to achieve. In such situations complementary examination procedures are required (eg. serial sections from formalin-fixed, paraffin-embedded tissue blocks, mounted on glass slides and usual stained with H&E, immunohistochemistry, molecular studies, electron microscopy, etc.).

Another method which can be used in thyroid pathology for diagnostic purposes is Second Harmonic Generation (SHG) Microscopy.

SHG microscopy is a label-free laser scanning

microscopy technique that exploits a nonlinear optical effect – the generation of the second harmonic in samples illuminated by an intense laser field [1, 2]. SHG can occur only from materials that do not have a center of symmetry, thus analyzing absolute molecular structure in organized organic environments, such as collagen fibrils, microtubules and the myosin chain of muscle cells. SHG microscopy has been proven to be a useful tool in biomedical tissue imaging [2] because it can be used for imaging endogenous structures like type I collagen [1] as well as for the characterization of collagen organization [3-5] and has been recognized as a promising approach for the diagnostics of different cancer types [6-8], by detecting collagen structure modifications [7].

The thyroid gland is wrapped in a thin fibrous capsule, from which originate numerous fibrous septae that penetrate the thyroid parenchyma and divide it into incomplete lobules (the so-called thyromeres). Macroscopically, the thyroid capsule seems complete, but it is incomplete from the microscopic point of view, as it adheres tightly to adjacent structures (laryngeal thyroid cartilage and trachea) [9].

Nodular enlargement of the thyroid gland comprises those situations in which one or more nodules are present. This presence of nodular enlargement is the most common in the case of non-toxic nodules, also known as adenomatous goiter or colloidal goiter.

Polinodular goiter with different-sized follicles can be a clinical manifestation of a wide range of different pathologies and not the expression of a single disease [10].

The usual classification of neoplasms of follicular epithelial cells are in benign (adenomas) and malignant (carcinomas) tumor proliferation. The benign ones are called follicular adenomas [11], which are encapsulated, non-invasive tumors showing evidence of thyroid follicular cell proliferation without the specific nuclear characteristics of thyroid papillary carcinoma [12].

Papillary Thyroid Carcinoma (PTC) is a malignant epithelial tumor, usually invasive, showing evidence of abnormal proliferation of thyroid follicular cells with characteristic nuclear changes: irregular contours and nuclear pseudoinclusions, nuclear membrane irregularities, and chromatin marginalization. For a correct diagnosis of the classical PTC, the papillary fibrovascular axes, the invasive character or the characteristic cytological features are required. [12].

The encapsulated variant of PTC is a type of proliferation with typical cytological and architectural changes, entirely surrounded by a thin, fibrous capsule that may be intact or infiltrated only focally by the tumor. If the capsule is invaded by the proliferation of malignant tumors, we are dealing with an aggressive form of PTC.

The encapsulated variant represents about 10% of all cases of PTC and has an excellent prognosis. Differential diagnosis is made with follicular adenoma with papillary hyperplasia [12].

Over the years, diagnostic criteria for follicular and papillary thyroid carcinomas have changed, but the two names have been retained. There have been several variants of papillary carcinoma for which the primary diagnostic criterion is based on nuclear features [11].

Some thyroid encapsulated neoplasms may present diagnostic difficulties due to the fact that only nuclear changes are sufficient to justify and diagnose PTC but there is the uncertainty about the capsular or vascular invasion. Encapsulated follicular tumors lacking the PTC nuclear characteristics are difficult to differentiate. For example, follicular carcinoma (a malignant tumor) can be distinguished from follicular adenoma (a benign tumor) only by demonstrating invasive character in the nodule capsule or capsular vessels [12].

We started from the idea that SHG can be used to observe three-dimensional structures of a tissue sample without the need for staining.

In this way, this method helps us in the correct diagnosis of encapsulated tumor entities that require complementary examinations from the pathologist or in order to determine a possible capsular structural change before the onset of malignant transformation of a benign encapsulated tumor.

OBJECTIVE

The purpose of this study was to use the collagen structure in the nodule capsule to obtain information on the follicular adenoma capsule and encapsulated papillary thyroid carcinoma (PTC) capsule for differentiating between benign and malignant thyroid nodules. The study was based on optical microscopy images and SHG microscopy, with the latter used for the visualization of type I collagen. We also show that the FFT analysis of the SHG images can provide information about the collagen fiber orientation.

MATERIALS AND METHODS

A batch composed of encapsulated-PTC and follicular adenoma tissue from 24 sections tissue samples (12 for Encapsulated-PTC capsules and 12 for follicular adenoma capsules) was used for this study. Sections of 4-5 µm were made from each paraffin tissue block. They were mounted on glass blades and stained with Hematoxylin and Eosin (H&E) and visualized with a light field microscope (Leica DM3000). The tissue architecture of the normal, benign and malignant regions of interest and the capsule surrounding the nodules have been identified. Unstained pairs of the H&E stained tissue sections were used for SHG imaging for collagen organization assessment.

SHG imaging was performed using a Leica TCS-SP confocal laser scanning microscope modified for nonlinear optical imaging [13]. We have used a mode-locked Ti:Sapphire laser operating at 780 nm and with ~150 fs pulses. A 40X, 0.75 numerical aperture objective was used to focus the laser beam on the sample, while the SHG signals were collected in the forward direction through a condenser lens. The average power reaching the sample plane was kept less than 15 mW and no photodamage was observed on the samples.

SHG images were used to estimate the collagen fiber orientation by FFT analysis using ImageJ software. For an image containing aligned fibers, we expect an FFT image with higher values along the direction orthogonal to the direction of the fibers and with an elliptic intensity plot. On the other hand, for an image with randomly oriented fibers, the FFT image intensity plot should be close to a circle. The FFT power spectra images were first binarized and then fitted with an ellipse. A collagen orientation index was calculated based on the length of the minor (S) and major (L) axes of the ellipse: $N = 1 - S/L$ [14]. Collagen orientation can thus be represented by an index ranging from 0 (random fibers) to 1 (aligned fibers).

RESULTS

Optical microscopy images of H & E stained sections do not give us information about the ultrastructure of the studied tumoral nodules capsule. The capsule appears as a fibrous structure surrounding the tumoral nodule. It looks identical to the follicular adenoma nodule and to the Encapsulated-PTC nodule. So this optic method is limited in terms of capsule study.

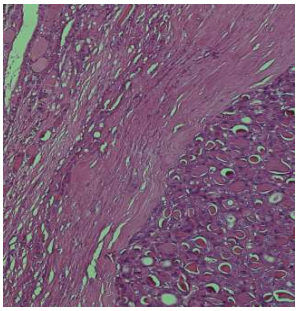
On the other side, the SHG helps to study the ultrastructural changes of the capsule. SHG highlights type I collagen in the capsule structure. So we can see if there are qualitative changes of this type of collagen from the two kinds of capsules. In addition, using FFT analysis of SHG images we can bring precious differentiation information of the two types of capsules: the follicular adenoma nodule or the Encapsulated-PTC nodule. We have noticed that in the Encapsulated-PTC nodule capsule there appears to be a collagen fiber organization as if they were trying to isolate malignant epithelial proliferation.

We acquired images with Second Harmonic Generation Microscopy which were used to assess the collagen orientation of tumoral capsular thyroid nodules previously diagnosed as benign or malignant by conventional H&E staining.

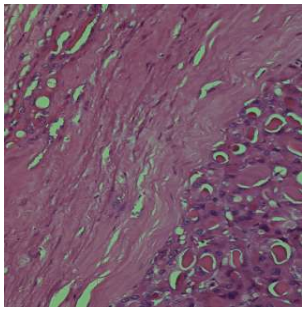
We compute the FFT spectra for the SHG images acquired for the considered pathologies. One can see that the average collagen orientation (N) computed from the FFT spectrum is higher for the follicular adenoma capsule ($N = 0.69$) than for the encapsulated-PTC capsule ($N = 0.4$). The FFT spectra were calculated for the entire images. We consider that if the spectra are computed for smaller regions of interest (ROIs), a distribution of values can be obtained, depending on the degree of alignment for the collagen fibers in the considered ROI. Averaging over a larger area, which is

also the case of the whole area analysis, it results in a lower N. Even though N was calculated on whole areas, the obtained results show a difference in collagen organization between the two capsules.

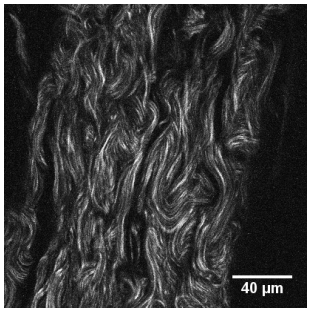
Figure 1. Follicular adenoma capsule



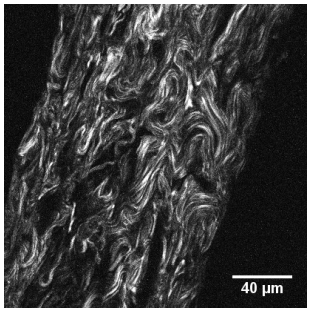
a). H&E 100x



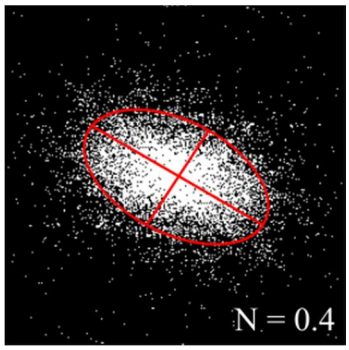
b). H&E 200x



c). SHG image 1

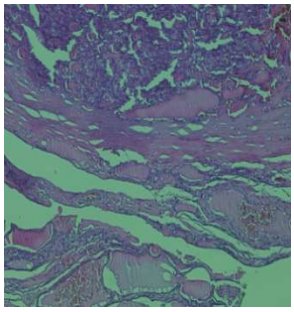


d). SHG image 2

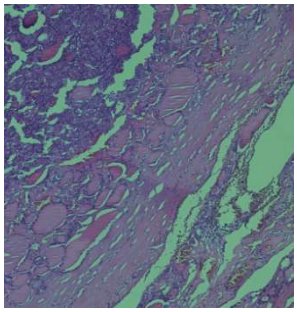


e). The FFT power spectra images - Follicular Adenoma Capsule

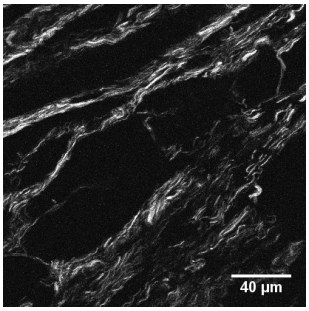
Figure 2. Encapsulated-PTC capsule



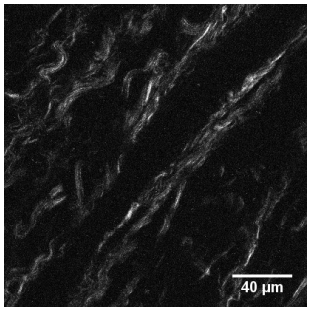
a). H&E 100x



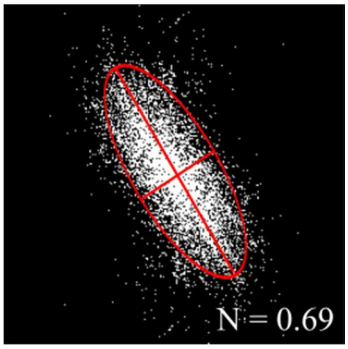
b). H&E 200x



c). SHG image 1



d). SHG image 2



e). The FFT power spectra images – Encapsulated-PTC Capsule

CONCLUSIONS

We found differences in the orientation of collagen fibers between the capsules surrounding benign nodules (follicular adenoma) and malignant ones (Encapsulated-PTC) by using SHG microscopy images and FFT analysis of these images.

Our research indicates that different collagen structures can be detected in the malignant nodules capsule (PTC) compared to the benign nodule capsule and the thyroid capsule.

Higher orientation was detected for the malignant capsule but that does not mean the collagen fibers are organized or that the malignant tissue organizes the fibers. We believe it is rather a defense mechanism that goes from the level of the thyroid adjacent stroma of tumoral nodules.

Future plans

The present study deals with the differential diagnosis between follicular adenoma versus encapsulated – PTC, since both are clear cases, thus making it easier to prove the validity of the theory regarding the reorganizing of the collagen fibers within the two types of nodules, as proven with SHG Microscopy.

Having completed that, the research may advance to analyzing less obvious situation:

1. Differential diagnostic between:
- Follicular adenoma versus follicular carcinoma;
- “Non-invasive follicular thyroid neoplasm with papillary-like nuclear features” (NIFTP) versus encapsulated papillary thyroid carcinoma with capsular invasion;
- Adenomatous nodule vs follicular adenoma.

2. Early detection of papillary carcinomas developed on follicular adenomas.

The SHG images can be developed as markers for use in clinical applications – a complementary method to early detection of suspected malignant nodules.

These above described microscopy methods help us distinguish between benign or malignant thyroid nodules, based on the capsular collagen organization.

Acknowledgements.

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Association of rare disease and acute intoxication – case report

Radu A. Macovei[1,2], Radu C. Ţincu[1], Mihail S. Tudosie[2]

Abstract: *Benzodiazepine overdose has various clinical manifestation, mainly regarding the central nervous system (CNS), cardiac and respiratory side effects, but rarely results in significant morbidity and mortality. Acute benzodiazepine poisoning results in dizziness, ataxia, nystagmus, dysarthria, hypoxia, hypothermia, bradycardia, hypotension, apnea, pulmonary aspiration, respiratory depression, coma, cardiopulmonary arrest and death. Anyway, deep nonresponsive coma should be investigated for additional etiologies. On the other hand, human transmissible prion disease has a fatal outcome with no specific treatment.*

Keywords: *prion disease, benzodiazepine intoxication, opisthotonus*

[1] Intensive Care Unit, Clinical Emergency Hospital Bucharest, Bucharest, Romania

[2] Carol Davila University of Medicine and Pharmacy, Bucharest

Human transmissible prion diseases are neurodegenerative disorders characterized by infectious pathogens accumulation with a long incubation period and devastating outcomes. A prion is defined as a small infectious agent lacking of nucleic acid, but containing protein [1]. It has an important feature regarding resistance to a number of decontamination procedures including processes affecting nucleic acids such as hydrolysis [2]. Up to present, human pathology recognize five related entities: Creutzfeldt-Jakob disease (CJD), Kuru, variant Creutzfeldt-Jakob disease (vCJD also known as new variant CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI) [3].

Prionopathies result from abnormal isoforms accumulation in the brain that leads to neuron apoptosis and important brain damage. Infective prion is a product resulting from defective folding of the normal prion, having the gene located on the short arm of the chromosome 20 [4]. Unfortunately, the prognosis is very poor in these patients, despite all efforts and sustained interventions.

Benzodiazepines are commonly used against various disorders such as insomnia and anxiety. They also are preferred agents for drug overdose, although their acute toxicity is low. Oral benzodiazepine intoxication rarely results in

significant morbidity and mortality. The body develops tolerance against such effects in the course of time and most common side effects are sedation and ataxia. Anxiolytic effects is rarely implicated in tolerance development. Acute benzodiazepine poisoning may result in dizziness, ataxia, nystagmus, dysarthria, hypoxia, hypothermia, hypotension, bradycardia, apnea, pulmonary aspiration, respiratory depression, coma, cardiopulmonary arrest and death.

CASE PRESENTATION

We present the case of a young white female, aged 26, admitted in our Toxicology – Intensive Care Unit of Clinical Emergency Hospital Bucharest from Bucharest, the capital of Romania. She was referred to us after deliberate ingestion of 200 mg benzodiazepine associated with 500 mg metoprolol. Ten months before this event the patient experienced complaints such as mood disorders, memory loss, irritability, inability every day social behavior and insomnia; initially, the condition was assessed as depression but no certain treatment was recommended. We couldn't find any history of visual hallucinations or tremor. Interview emphasized multiple study visits in the United Kingdom and occasionally intravenous abuse substances dependence. Any other past medical data were unremarkable. The first medical examination revealed a conscious patient, mild agitated, stable vital signs, with unusual hyperosmia and visual impairment. Toxicology assessment was positive for benzodiazepine in the urine, detected with fluorescence polarization immunoassay method; toxicological screening was negative for other drugs. She had a rapid unfavorable evolution the following hours after admission experiencing degenerative progression of psychomotor and cognitive functions, lack of hand-eye and alternating hand coordination, left hand tremor and left lower extremity weakness and in the end, ten hours after ingestion, she developed impressive opisthotonus and deep coma that required mechanical ventilation. The evolution was unexplained by her toxicological status and occurred unexpectedly.

Brain tomography was in normal ranges (Figure 1). She was performed lumbar puncture and the cerebral fluid features included clear aspect, normotensive, with glucose and electrolyte levels within normal limits and no type of cell detection. Regarding highly suspicion of tetanus, due to her occasionally intravenous drug administration, the infectious disease evaluation indicated anti-tetanus serum therapy, but clinical evolution wasn't improving. After 48 hours of nonresponsive evolution a new brain CT scan identified massive cerebral edema. Cranial MRI showed marked cerebral atrophy in frontoparietal areas, DWI hyperintensities (cortical ribboning) in basal ganglia bilaterally and diffusion restriction in these areas suggesting progressive multifocal leukoencephalopathy, whereas putamen and caudate nucleus were free of signal intensity (Figure 3). Considering these aspect, we performed PCR for the detection of JC virus which was negative. A prionic disease was highly suspected and 14-3-3 protein immunoassay on CSF was positive. The patient died after 2 months in Critical Care Unit due to multiple dysfunctions, with the diagnostic of Creutzfeldt-Jakob disease.

DISCUSSION

As a part of the prionic disease family, CJD evolution is characterized by rapid evolution and neurological deterioration. The majority of cases are represented by sporadic human prion diseases, while 1-2% of the remaining are infectious forms acquired from an established source with the prion disease and 5-15% is represented by the autosomal dominant type [1]. The presented case exhibits most of the sporadic CJD clinical features with rapid cognitive decline and mioclonus; MRI was an indispensable tool for differential diagnosis considering that DWI hyperintensities in the putamen, caudate and cortex have a high specificity for sporadic prion disease [6]. However, the short dramatic course of the disease and detection of protein 14-3-3 in CSF adds value to diagnostic criteria. The literature shows that the mean age of onset is around 65 years of age with a very short median survival time around four months [7], but we report an extreme age (eg. 26 years old).

CONCLUSIONS

The case presented in this paper was meant to describe the clinical progression of a rapid evolving encephalopathy in a patient admitted for benzodiazepine ingestion. It also underlines the importance of keeping an open mind when dealing with unexpected and unusual evolution of acute intoxication.

Figure 1. The first CT scan within normal ranges

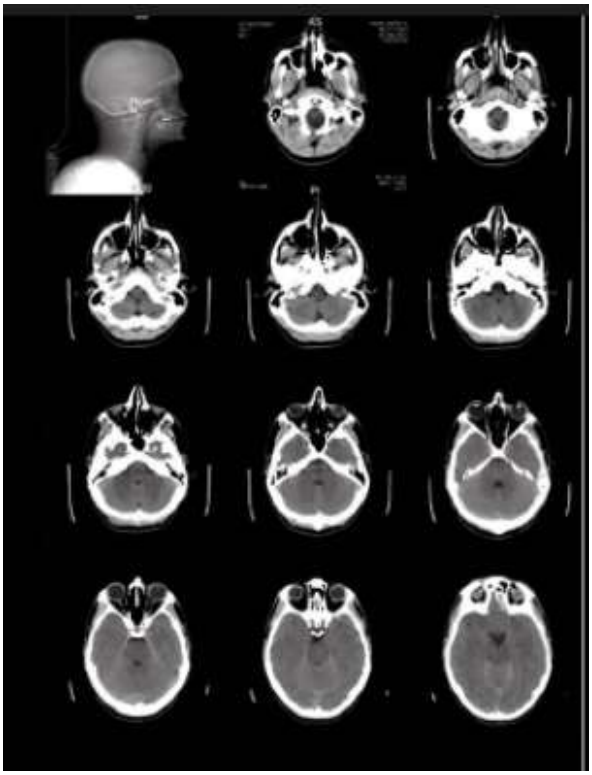
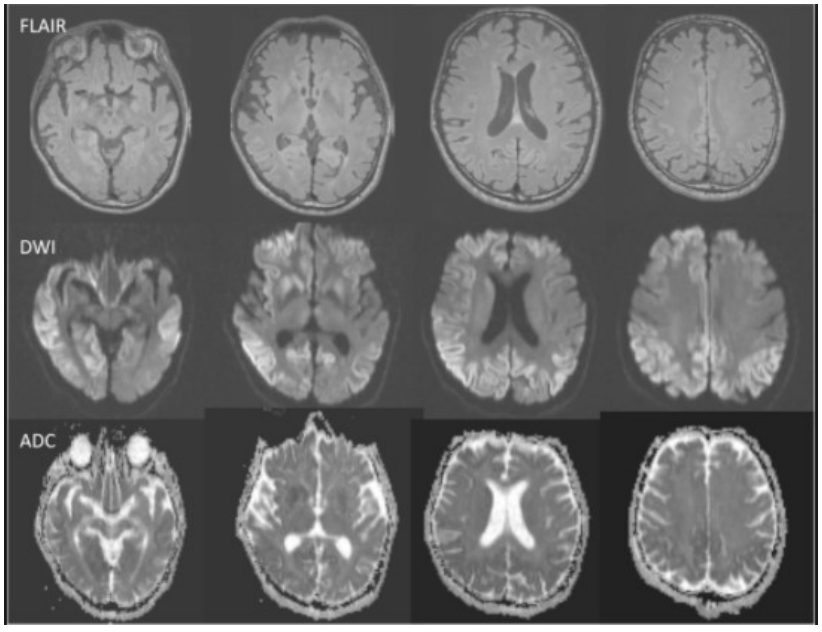


Figure 2. Cranial MRI showing cerebral atrophy, DWI hyperintensities (cortical ribboning) in basal ganglia bilaterally and diffusion restriction in these areas suggesting progressive multifocal leukoencephalopathy, whereas putamen and caudate nucleus were free of signal intensity



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Clinical aspects in implant fixed prosthodontics oral rehabilitation. Case report

A.M.C. Țâncu[1], E. Preoteasa[1], C. Preoteasa[1], M. Pantea[1], M. Meleșcanu Imre[1]

Abstract: *Benzodiazepine overdose has various clinical manifestation, mainly regarding the central nervous system (CNS), cardiac and respiratory side effects, but rarely results in significant morbidity and mortality. Acute benzodiazepine poisoning results in dizziness, ataxia, nystagmus, dysarthria, hypoxia, hypothermia, bradycardia, hypotension, apnea, pulmonary aspiration, respiratory depression, coma, cardiopulmonary arrest and death. Anyway, deep nonresponsive coma should be investigated for additional etiologies. On the other hand, human transmissible prion disease has a fatal outcome with no specific treatment.*

Keywords: *implants, osseous integration, staging, fixed prosthesis*

[1] Faculty of Dentistry, Carol Davila University of Medicine and Pharmacy, Bucharest

INTRODUCTION

Each year endoosseous dental implants gain greater acceptance among clinicians and patients. This has come about for several reasons, including excellent success rates published in long-term studies, improvements in fixture and abutment designs, more predictable surgical placement techniques, and increased consumer desire to have tooth replacement. Regardless of the implant system, the placement and functional success of endo osseous implants is greater than 90%) [1]. Fixed prosthodontic on implants is the most desirable treatment for the patients among the treatments on implants. When transforming a partially edentulous patient in a complete edentulous one, the transition difficult period can be avoided by keeping some teeth for fixed provisional, until the osseous integration of the implants is accomplished and the final prosthetic can be done [3]. In this regard, the importance of restoring patients with functionality during the implant healing period has grown in recent decades [7].

This paper presents a staged protocol of the patient's treatment that made the case easier to manage and offered a better comfort in the transition period.

All the authors have equally contributed to the article

Corresponding author: Mihaela Pantea
mihaela_pantea@yahoo.com

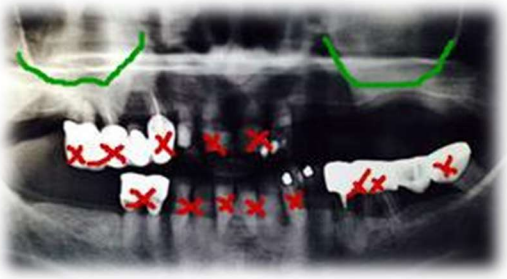
CASE REPORT

Material and method

T.S., a 66 years old female patient, with a general medical history of chronical C hepatitis, presented with a mucocell in the sinus cavity and a T,L-T maxillary edentation and L-T mandibular edentation, with inadequate fixed restorations, both in upper and lower jaw. An accurate and complex clinical examinations wad performed, including the prosthodontic, implant – surgical assessment, panoramic radiograph and computed tomograms for both jaws. The intermaxillary relationships were carefully examined and the OVD was recorded (5.7 cm).

A comprehensive treatment plan was proposed and decided, following the conclusions from the diagnosis findings. Thus, all the remaining teeth were in a poor dental status and needed to be extract, but in a staged approach, as in figure 1.

Figure 1: Initial dental status



The 1st step was the surgical one on the maxillary arch. So, after CT, Rx measurements and evaluation of bone volume and density related to prosthetic planning dental implants position was decided the placement of 3 implants (Superline, Dentium) (2.2/2.4/2.6). Prior to this was performed the left sinus mucocel evacuation. Meantime was performed also the internal sinus lifting with mineral bone grafting (Osteon, Dentium).

The 2nd surgical step. After the healing period (2 months), right sinus lifting was performed with same materials and were placed 3 implants (1.4/1.5/1.6).

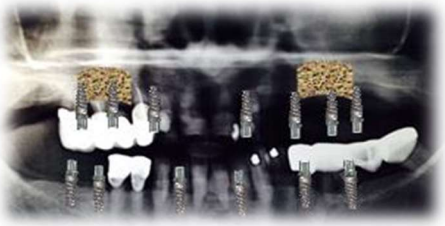
By the time of implants osseous integration, the 11 and 21 were kept in order to provide patient's minimal aesthetic and functional comfort. Provisionals, immediate loading – nor fixed or removable couldn't be used due to bilaterally sinus lifting with bone grafting materials and the bone density. (Figure 2)

Figure 2: The clinical situation before the 3rd step

Meanwhile the 6 upper jaw implants osseous integration, the 3rd surgical step, consisted in the placement, on the lower jaw, of 2 implants (4.6/4.7) and 1 implant in the upper jaw (1.2), all of them prosthetic driven. After the evaluation of the occlusal vertical dimension (OVD) that we recorded and preserved, the vertical space was assessed as well as mandibular implants positioning in order to obtain correct occlusal relationships.

In the 4th surgical step the insertion of 2 frontal mandibular implants (3.2/4.2) and 2 left lateral mandibular implants (3.4/3.6) was performed. 3.3/ 3.4/4.3/4.4/4.5 for fixed provisional. The extracted teeth were: 1.2/1.3/1.5/1.6/2.2 initially and just before the implants uncovering, 1.1 and 2.1, in the upper jaw and 3.1/3.2/3.5/4.1/4.2/4.6/4.8 in the lower jaw and 3.3/3.4/4.3/4.4/4.5 were used for provisionals. (Figure 3)

Figure 3: Panoramic radiograph after the implant's placement



RESULTS AND DISCUSSIONS

Due to the case complexity, because of the surgical aspects (13 implants insertion), bilaterally internal sinus lifting with bone grafting and the evacuation of a

mucocell, related to the prosthodontic ones, meaning the complete fixed bimaxillary rehabilitation, have made the treatment to last 1,5 years until the final prosthetic rehabilitation that we will describe next.

Due to the staged surgical approach, there was no possibility to split the final prosthetic work in more segments, nor in maxilla or mandible, so we produced 2 full – arch restorations on implants.

The idea of the final prosthetic treatment was to rehabilitate simultaneously the 2 jaws in order to split optimally the vertical prosthetic space. So, after all implant's uncovering and the last teeth extraction the healing abutments were applied and after 10 days the impression was taken. Monopren transfer (Kettehbach) was used as impression material, in an open individual tray technique, using transfer abutments.

The work casts were obtained with the analogue implants in their position. On this casts, occlusion rims were made for the intermaxillary relationship registration. All the steps were performed in order to establish accurately the occlusal and intermaxillary relationships: the vestibular curve of the upper occlusion rim was esthetical and phonetic established.The occlusal plane's level and direction were established using the usual methods and also the patient s youth photo, that provided a lot of useful information, such as the visibility of the 6 frontals. The initial correct OVD was kept and the 2 rims were fixed in the correct CR position. The information about the facial midline, the smile line and canine lines, together with other information regarding the teeth colour, size, form, arrangement and positioning were transmitted to the laboratory.

After the intermaxillary relationship registration, the dental lab produced the metal frame of the prosthetic work. The trial of the metallic part was done related to the axial and cervical marginal fit. With the patient s agreement, the last esthetical decision were taken, regarding the colour and form of the artificial teeth, to provide the dental lab all the information for the ceramic application. In the dental lab Vita ceramic layers were applied.

The try-in of the prosthetic work was done, aesthetic, phonetic and occlusal relationships and intermaxillary, horizontally and vertical. Also, occlusal adjustments were performed. Then the 2 fixed prostheses were glazed and polished.

The final work was provisional cemented and then definitively (Figure 4).

Figure 4: Final result

Figure 5: A 3 year follow up

Figure 6: Final occlusal relationship

The follow-up was done, after 6 months and then after 3 years, and the results can be observed on the panoramic radiograph and indicates a very good situation.

CONCLUSIONS AND CLINICAL IMPLICATIONS

For many patients, as for the patient s case that we described previously, the transition between the dentate state and the completely edentulous state, with removable provisional is difficult to accept. That s why we choose a staged approach for our case, with strategic extractions and implants applied in 4 surgical different phases. The provision prosthetic was a fixed one, the major advantage of this treatment protocol. The treatment planning in such complex cases represents a challenge for the implantologist and prosthodontist and for the patient and our presented protocol facilitates the transition from a destroyed dentition to a full-arch reconstruction.

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Occipital radionecrosis and neuroplasticity in astrocytoma

Carmen A. Sirbu[1,2], Octavian M. Sirbu[3], Alexandra E. Bastian[4,5]

Abstract: *Background: Late-delayed complications after radiotherapy (RT) results from an imbalance between cell lesions and the protective capacities of the CNS. Temozolomide (TMZ) after RT may represent a potent radiosensitizing regimen. Although radionecrosis (RN) of the anterior visual pathway has been documented, in our opinion this is the first report of reversible visual field loss associated with occipital lobe radionecrosis.*

Case observation: We report a patient who suffered a left lateral homonymous hemianopia one year after radiochemotherapy (RCT) for an infiltrative low grade fibrillary astrocytoma. The visual field deficit was completely reversible after one month. Visual field defects have been described after the use of conventional external beam therapy for lesions near the anterior visual pathway. The cortex is relatively spared after RT.

Conclusions: Given the new scientific data, we suppose that neuroplasticity may play a role in the reversibility of visual field deficit. At this time there is no proven treatment of radionecrosis. Homonymous hemianopia caused by occipital lesions are attributable to vascular disease and tumors, but take into account radiation effects. The risk of neurogenic visual loss must be factored into the decision to irradiate the whole brain.

Keywords: *fibrillary astrocytoma, temozolomide, radiation necrosis, visual recovery, neuroplasticity*

[1] Department of neurology „Carol Davila" Central Military University Emergency Hospital, Bucharest

[2] Titu Maiorescu University, Bucharest

[3] Neurosurgery Department, Rouen University Hospital Center

[4] Carol Davila" University of Medicine and Pharmacy, Bucharest

[5] Department of Pathology, Colentina Clinical Hospital, Bucharest

INTRODUCTION

Radiation therapy is an integral part of modern therapy in gliomas. Early or delayed side effects are taken into account in determination of the therapeutic algorithm of each patient. The combination of radiotherapy and chemotherapy further increases the vulnerability to side effects. In this context, we present the case of a young woman diagnosed with fibrillary astrocytoma. One year after combined radiotherapy and chemotherapy with Temozolomide, right occipital lobe radionecrosis with impaired vision appeared.

Although such cases cited in literature are irreversible, in this case, both visually campimetric deficit and occipital brain lesion were fully reversible.

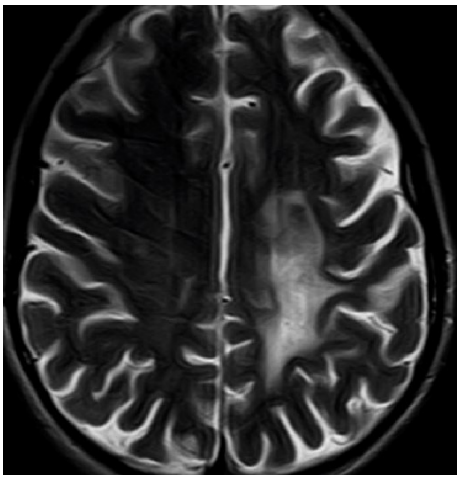
Corresponding author: Carmen A. Sirbu
sircar13@yahoo.com

MATERIAL AND METHODS

A 21 years old, right-handed Caucasian female with mild idiopathic thrombocytopenia presented to the hospital with right sensory-motor hemiparesis. MRI revealed a subcortical low grade glioma in left rolandic region, extended to basal frontal and ascending parietal white matter regions, invading the dominant arcuate fasciculus, confirmed by brain biopsy.

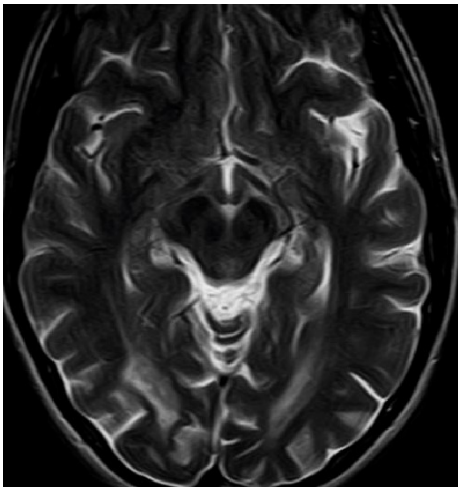
Given the infiltrative character of the tumor and its deep location, a surgical intervention is considered risky (the tumor invades left pyramidal fibers, thalamocortical fibers and superior longitudinal fascicle), especially without perioperative functional cortico-subcortical cartography procedures. Our patient undergoes 64Gy (photon teleradiation) radiotherapy for 6 weeks, followed by chemotherapy with Temozolomide (TMZ), 250 mg/day, 5 days/month for 6 months. Conventional MRI control reveals stationary aspect of the tumor (figure 1).

Figure 1



One year after chemotherapy, the patient insidiously develops left lateral homonymous hemianopia. A new conventional brain MRI shows a new 26/10 mm, irregular, non-homogenous, imprecisely defined right occipital lesion with hyperintense T2/Flair and isointense T1 signals, without contrast media enhancement. Fluorodeoxiglucose (FDG) PET-CT scan allows the differential diagnosis between tumor growth or radionecrosis and it reveals significantly decreased FDG uptake in the right occipital region, including the visual cortex (figure 2).

Figure 2

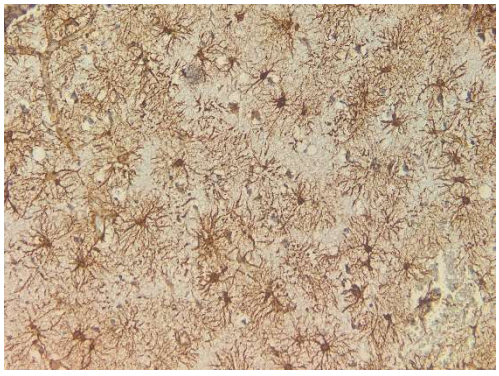


RESULTS

We conclude that the visual field deficit is the result of cerebral radionecrosis. The patient started a short period of corticoid treatment, with no improvements. One month from the first appearance of the hemianopia, it completely remitted and occipital right lesion were not visible.

Worsening deficit in patients with cerebral tumors may suggest either tumor progression or its recurrence [1]. Imagistic methods reveal edema and enhanced lesions near the tumor area. On the other hand, radiotherapy may determine effects after months or years and these are called late-delayed reactions [2].

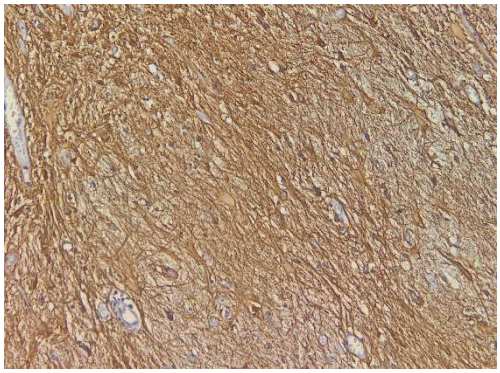
Figure 3



One of them is radionecrosis that occurs by vascular changes and ischemia, increase of capillary permeability and cerebral edema. Due to capillary permeability disturbances, adverse reactions of

chemotherapy appear earlier and are more severe (figures 3, 4). Necrosis can be a result of radio and chemotherapy combination [3].

Figure 4



Temozolomide (TMZ) amplify the answer to radiations through DNA modifications and apoptosis [4]. TMZ combined with radiotherapy, enhances blood-brain barrier damage, leading to increased concentrations of therapeutic agents [5].

DISCUSSIONS

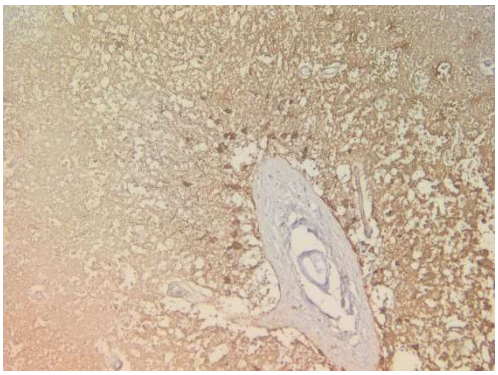
Few things are known about radionecrosis because it is difficult to differentiate from the tumor relapse with imaging techniques [6] and because the rate of surgical secondary interventions and brain autopsies are low in these patients [7].

In a study of 426 patients presenting glioma, Ruben and co. prove that the average time for the first appearance of necrosis is 11.6 months [8]. Also, adjuvant chemotherapy rises to over 4 times the cerebral necrosis risk. Peterson and co. reported a 2.5% incidence of radionecrosis, 8-31 months post-radiation, in a study including 200 patients with radiated and chemo-treated cerebral tumors [9]. So, as many have already demonstrated, chemotherapy has an amplifying effect in cerebral radionecrosis development. The incidence of radionecrosis is slightly raised in anaplastic oligodendroglial tumors than anaplastic astrocytomas and this is an argument for glial theory and its role in radionecrosis occurrence.

Things are even more complicated because the edema associated to this pseudoprogression is as symptomatic as the tumor actually progresses [10]. Conventional MRI (T2 and T1 with contrast) is limited in differentiating between tumor relapse and RT induced necrosis. Unfortunately, in many Gad positive lesions that occur after combined treatment, there are necrosis lesions and viable tumor cells and molecular magnetic resonance imaging of endogenous proteins and peptides are not for current use [11]. Diffusion MRI measures the mobility of water from tissues into the cells. After treatment, tumor cells are dehydrated and have a high apparent diffusion coefficient (ADC). Decreases of ADC indicate high cellularity [12]. Magnetic Resonance Spectroscopy detects tumor metabolites from tissues (choline, creatinine, lactate, lipids, N-acetyl aspartate) and is more sensible [13]. Dimensional spectroscopy has superior sensitivity indicating a relapse based on raised choline/NAA and choline/creatinine ratios [14].

18-Fluorodeoxyglucose PET scan is useful for differentiating between radionecrosis and recurrence and is 81-86% sensitive and 40-94% specific [15]. Still, false positive results have been encountered in non-malignant inflammatory processes, electric epileptic seizures and healing processes up to 3 months post-surgery. Even though, radionecrosis activates healing mechanisms and raises the glucose metabolism. This is why MRS is superior. There are some mechanisms that can explain postradiation necrosis: DNA modifications, coagulation factors imbalance with thrombosis facilitation [16]. The main mechanism of radionecrosis is associated with oligodendroglia injury or vascular endothelial damage (figures 5, 6).

Figure 5

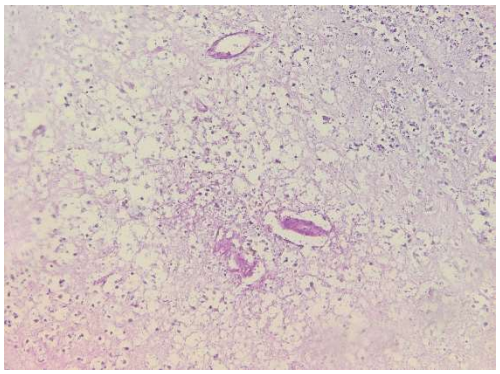


As a result, white matter tissue is often affected than gray matter tissue. Cytotoxic edema and tissue necrosis are the consequence of imbalance between

tissue plasminogen activator and urokinase plasminogen activator.

But an autoimmune mechanism may be also involved.

Figure 6



Anterior visual pathways necrosis was well documented, especially in pituitary tumors, craniopharyngioma, parasellar meningiomas or optic nerve tumors [17]. In generally, visual field defects occur after one or more years after the radiotherapy stopped. Corticosteroids, surgery, bevacizumab and Hyperbaric Oxygen Therapy (HBO) are all possible good treatment options for symptomatic RN. The treatment goal is to provide the patient with resolution of neurologic symptoms, with the least toxicity and invasiveness [18]. Corticosteroid therapy was used to diminish the cerebral edema and cytokine release after radiation. Hyperbaric oxygen is considered to be useful in raising the tissular oxygen supply and for initiating tissue healing.

Diffuse, infiltrative, low grade gliomas (LGG) represent a clinical, histopathological and molecular distinct group with a very controversial management [19]. LLG patients may survive up to 20 years from the moment they were diagnosed, but there is the risk of tumor evolution into higher grades, eventually leading to neurological deficits and death [20]. Diffuse astrocytomas include the fibrillary, gemistocytic and protoplasmic types [21]. The fibrillary one is the most widespread and it presents a homogenous cellular population and moderate uncharacteristic nuclear modifications. Mitosis rate in grade II OMS astrocytomas is very small [22]. Clinically, the patient presents epileptic seizures, focal deficits occurred after many years and intracranial high pressure, especially in the subtentorial and intraventricular location. Conventional MRI is useful for guiding the biopsy and the resection, for radiotherapy and treatment monitoring. The usual method is MRI without contrast media, but when we add contrast it reveals changes in tumor grade transformation, better. In LGG spectroscopy shows high choline (high turn-over) and low NAA, reflecting neuronal loss [23]. Even though, similar results can be seen in non-tumor lesions. MRI is used rather for guiding the biopsy in an intense active area than for monitoring the evolution. 18 Fluorodeoxyglucose PET scan has a limited value as long as LGG indicates a low caption comparative to normal cortex [24]. The role of PET-FDG is, however, demonstrated in differentiating radionecrosis from tumor recurrence. More frequently used are [11C] methionine-PET scans given the fact that methionine is captured by tumor cells showing their proliferation process, thus giving a better contrast. PET-MET is also used for differentiating LGG from non-tumor lesions [25].

Neuroplasticity defines the ability to regain function after a neuronal lesion due to neuronal structures that take over the function of the damaged area and to nervous tissue reorganization (that is based on formation of new connections between neurons and/or new cell synthesis). The theory imposed in 1920 by S. Ramon y Cajal (which stated that once the development stopped, growth and regeneration of the axon and dendrites irrevocably stop) is torn down discredited by present scientific data [26]. Altman and co. showed the ability of some brain areas (such as hippocampus and olfactory bulb) to generate new neurons and they called this process neurogenesis [27]. Later, proves appeared that shown this process is influenced by factors like age, stress, physical condition [28].

Multipotent stem cells divide periodically in our brain giving birth to other stem cells or to adult cells. The newly formed stem cells move into areas that allow maturation. Approximatively 50% of them will die without reaching maturity. The others will become glial cells or neurons depending on the necessities of the brain area where they migrated. Fred H. Gage, emphasized in his review, that the necessary time for a stem cell to become functional and adapted to brain

is about a month [29]. In this way we could explain full recover of the patient with left lateral homonymous hemianopia a month after the debut. A series of growth neuronal factors play an important role in keeping stem cells alive, mature and functional. Regaining cortical functions can be somehow explained by reorganization of cortical areas [30]. This process takes also place in the areas near the lesion or near the contralateral homologous cortex. Visual cortex reorganization after focal lesions implies plasticity mechanisms accompanied by excitation/ inhibition imbalances and changes in dendritic and axonal divisions [31]. Studies demonstrated a decrease in GABA inhibition and a growth of glutamate answer mediated by NMDA receptors in adjacent areas with the afflicted visual cortex [32].

CONCLUSIONS

Combined radiation and chemotherapy rises many times the cerebral necrosis risk, which may occur months or years later. Patient management should use specific and sensitive diagnostic tests. The differential diagnosis between tumor recurrence and radionecrosis is very important. Based on this differentiation, therapeutic attitude is different. For diagnosis certainty, tumor molecular biology tests are very useful, especially that current imaging techniques still cannot make a clear distinction. Low-grade gliomas should be better supervised by complete excision of the tumor, where the situation allows. Other therapeutic interventions, like chemo and radiotherapy, especially in the early years of evolution, should be used with caution, given their unpleasant effects. Radionecrosis should be treated promptly with corticosteroids, surgery, hyperbaric oxygen or bevacizumab.

Also, we need a plan for neurorehabilitation that assist in the neuroplasticity. All these compete to increase life expectancy and quality of life.

Conflict of interests

The authors declare that they have no conflict of interests.

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Departamentul Profesional-Ştiinţific
Email: profesional@cmr.ro
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Asociația Medicilor și Farmaciștilor Militari din România

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Cu stimă,

Vicepreşedinte
Dr. Călin Bumbuluţ
Coordonator al Dep. Profesional-Ştiinţific

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