Original paper

Associated anaplastic large cell lymphoma (bia-alcl) with silicone breast implants

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Abstract

Non-Hodgkin’s lymphoma of the breast is extremely rare. Most of these lymphomas are type B, including large B cell diffuse lymphoma, extra-nodal marginal lymphoma, follicular lymphoma, primary effusion lymphoma and lympho-plasma-cytic lymphoma. BIA-ALCL is negative anaplastic lymphoma kinase (ALK) and is characterized by cells with horseshoe-shaped eccentric nuclei called “hallmark cells”. Unlike other types of ALCL, BIA-ALCL rarely invades your breast in depth. By contrast, non-Hodgkin’s T-cell lymphoma (NHL) found in breasts without implants is mostly B cell lymphoma. Due to the increasing number of cases and the fact that the first case also appeared in Romania, we consider it advisable to take information and prevention measures as well as to adopt a treatment protocol in our country. The present paper aims at adopting a unitary diagnosis and treatment protocol for all plastic surgeons. We also consider it advisable to inform patients before surgery on risk. Through this paper we want to propose a national protocol to follow and also to argue its choice.

Keywords

Silicone, breast, lymphoma, implants, BIA-ALCL.

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Associated anaplastic large cell lymphoma (bia-ALCL) with silicone breast implants

Introduction

Non-Hodgkin’s lymphoma of the breast is extremely rare. Most of these are type B, including large B cell diffuse lymphoma, extra-nodal marginal lymphoma, follicular lymphoma, primary effusion lymphoma and lympho-plasma-cytic lymphoma (AL-Rohil & al [1]). T-cell peripheral lymphoma represents only 10% of all breast lymphomas. In breast implant patients, over 90% of these are anaplastic lymphoma kinase (ALK) compared to breast implant-free patients with only 37% (ALK- (Bijjak & al [2]).

The appearance of high-cell anaplastic lymphoma in patients with mammary implants is a novel issue. Today, about 1.7 million mammary implants are performed each year around the world. To date, over 500 cases of BIA-ALCL have been reported in the world, of which 16 deaths (Kricheldorff & al [3]). BIA-ALCL may occur one year after breast augmentation/reconstruction up to 32 years after that (Story & al [4]). The average duration of implant exposure varied on average from 7 to 13 years. The incidence of BIA-ALCL is estimated at 2.03 per 1 million people, or 1 per 30,000 women with breast implants (Doren & al [5]). The first case of BIA-ALCL was published in 1997 by Keesh & Creech (Keech & al [6]). In 2016, the World Health Organization defined BIA-ALCL as a distinct entity (Swerdlov & al [7]).

Anaplastic large cell lymphoma (ALCL) subtypes can be grouped according to the presence or absence of surface receptors for ALK and also the primary site of tumour development in cutaneous ALCL and ALCL associated with mammary implants BIA-ALCL (Chihara & al [8]).

- Primary systemic ALCL: anaplastic lymphoma kinase (ALK) positive
- Primary systemic ALCL: ALK-negative
- Primary cutaneous ALCL (PC-ALCL)
- BIA-ALCL: ALK-negative, CD30 positive

Large-cell anaplastic lymphoma (ALCL) represents approximately 2-3% of all non-Hodgkin T-cell lymphoma (NHL) peripheral lymphoma [9].

BIA-ALCL is negative ALK and is characterized by cells with horseshoe-shaped eccentric nuclei called “hallmark cells”. Unlike other types of ALCL, BIA-ALCL rarely invades your breast in depth. By contrast, non-Hodgkin’s T-cell lymphoma (NHL) found in breasts without implants is mostly B cell lymphoma.

Most often, BIA-ALCL manifests itself as an encapsulated peri-prosthetic serum and can rarely develop as a solid tumour that can infiltrate the thoracic wall or the large pectoral, in which case the prognosis depends on the invasion of the loco-regional ganglia. The cause of this type of tumour remains uncertain. It appears to develop against a background of chronic inflammation or toxins coming out from the implant. The presence of the subclinical bi-film on the implant surface, the capsular contracture, the direct implant toxicity, and the host’s immunological response are considered as contributing factors in the development of BIA-ALCL (Kaartinen & al [10]). From the treatment point of view, it is generally acknowledged today that in the incipient stages, simple capsulectomy is sufficient to eradicate the disease, while advanced stages include chemotherapy.

Materials and Methods

Due to the increasing number of cases and the fact that the first case also appeared in Romania, we consider it advisable to take information and prevention measures as well as to adopt a treatment protocol in our country.

Thus, as a measure of information we have introduced in the assumed consent of patients information about BIA-ALCL: what it is, how it manifests itself, how it is treated and how it can evaluate.

As a preventative measure, we decided to use almost exclusively smooth implants, and we recommend patients an annual breast ultrasound. We also explain to patients what the first signs are and when they should come to us for a consultation.

Until now, although initially patients have a retention in making breast augmentation, in the end there were no patients to give up this procedure. The present study relates to a number of about 60 patients, since the information about BIA-ALCL was introduced in the information consent.

Regarding the diagnosis and treatment protocol, we decided to follow the NCCN protocols reported in figures 2 and 3. However, we also recommend annual mammary ultrasound even in the absence of any signs or symptoms.

Results and Discussion

Since 1997, cases of ALCLs associated with mammary implants have been published, so in 2011 the FDA was aware of 63 cases of BIA-ALCL. However, at that time, a number of breast implants around the world were estimated at around 5-10 million, and the Food and Drug Administration (FDA) considered the 63 cases irrelevant (Swerdlov & al [11]). Only in 2016, the World Health Organization (WHO) recognizes this pathological entity as a distinct one associated with the presence of mammary implants, and one year later the FDA recognizes this pathogenic entity, 414 cases of BIA-ALCL known worldwide and 9 deaths (Administration UFaD [12]). At that time, a new pathology of non-Hodgkin’s anaplastic lymphoma associated with the presence of breast implants -ALCL was defined and accepted. Since 2017, the FDA has named this new form of non-Hodgkin anaplastic lymphoma as BIA-ALCL. There have been numerous studies in different countries, with more and more BIA-ALCL cases reported: 41 in the UK (Johnson & al [13]), 22 in Italy (Campagnale & al [14]), 43 in the Netherlands (De Boer & al [15]), 19 in France (Laurent & al [16]), 7 in Germany (BFAm [17]) and 149 in the United States (Doren & al [5]). Until now, no BIA-ALCL case has been confirmed in Romania, but no screening study has been conducted. The exact incidence of BIA-ALCL numbers is very difficult to estimate, but the opinion of some experts shows that in Australia and

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New Zealand the incidence would be 1: 2832 for women with polyurethane implants, in the UK 1: 24,000 and in the US incidence would be 1: 30,000 (DOREN & al [5]; LOCH-WILKINSON & al [18]). In 2016, with the acknowledgement by the WHO of BIA-ALCL as a distinct pathological entity, the National Comprehensive Cancer Network (NCCN) developed the first diagnostic and treatment guide for BIA-ALCL (SWERDLOW & al [7]; CLEMENS & al [19]). For over 25 years, NCCN has been developing diagnostic and treatment guidelines for various forms of cancer in the US, all of which have been recognized by both the FDA and the WHO (CLEMENS & al [20]). NCCN clinical guides are always up to date data and research, so we can consider this guide as the gold standard in treating BIA-ALCL (CLEMENS & al [21]).

1. Ethiology and physiopathology

One of the possible causes seems to be the presence of infection or chronic inflammation, although breast augmentation with silicone prostheses is considered an aseptic surgery. However, there is research that supports the association between chronic inflammation and NHL (DU & al [22]) and, on the other hand, the association between BIA-ALCL and various infections (LOCH-WILKINSON & al [18]). Thus, a textured implant creates a biofilm due to bacterial colonization, which will cause the increase in the number of T lymphocytes; they will determine the appearance of the serum and later of the lymphoma (ADAMS & al [23]). Chronic infection is considered to be a contributing mechanism in some types of human lymphoma. It is assumed that a cytokine-rich environment facilitates the rapid division of host lymphocytes, causing tumour alterations leading to BIA-ALCL. The cytokine profile of BIA-ALCL cell lines, specifically interleukin (IL)-6, transforming growth factor (TGF)- and interleukin (IL)-10, has also been shown to induce populations of immune suppressive cells that can inhibit host immunity and facilitate the development of cancer. Also, receptors were found in BIA-ALCL-developed cell lines for (HLA-DR, CD80, CD86), IL-2 (CD25, CD122) and IL-6 (STEWART & al [24], KADIN & al [25]). Although there has been no direct correlation between chronic infections and BIA-ALCL until now, there are reported cases of association between Ralstonia and BIA-ALCL (HU & al [26]). Another pro argument that supports the association between a possible infection and BIA-ALCL is the presence of CD30. This is a protein that is normally found on activated T cells and is essential in the diagnosis of BIA-ALCL. In support of biofilm infection/modification theory, there is also chronic Helicobacter pylori infection that promotes the appearance of gastric lymphoma (WANG & al [27]) but also possible cutaneous microbiome changes induced by direct or indirect mechanisms having as a model the lymphocytes produced by Borrelia species (FITZAL & al [28]) as well as possible alterations of the gut microbial by direct or indirect mechanisms like it shows in “Figure 1”. Therefore, it is plausible that chronic infected mammary implants mediate inflammatory and neoplastic processes, resulting in the development of a T cell lymphoma. In conclusion, although underestimated the association between inflammation / chronic infection and the appearance of BIA-ALCL, however, a 14-point protocol was issued consisting essentially of perioperative and localized antibiotic treatment, immediate implant exposure to the air, preventing implant skin contact and drainage tube omission, and which aims at minimizing the risk of infection or chronic inflammation on the implant (ADAMS & al [23]). In general, the BIA-ALCL determinism on the background of a chronic inflammation/infection can only occur in genetically susceptible persons.

Figure 1. BIA-ALCL pathophysiology of inflammatory/infectious etiology.
Modified and adapted after F. FITZAL & al [28].
Another possible cause would be the allergic determinism of BIA-ALCL. Eosinophils were found in implant capsules, and tumour cells expressed the GATA 3 transcription factor and produced IL13, suggesting the possible development of BIA-ALCL on an allergic background (KADIN & al [29]).

Lately, more and more genetic studies have been done on BIA-ALCL, starting from the previously known data on genetic determinants of malignant blood diseases. According to the latest studies, activation of STAT3 mutations was detected in 64% of cases, and in 25% there was also a truncating mutation of SOCS 1, which is supposed to trigger the JAK / STAT pathway by losing negative regulation. There are multiple activation pathways of STAT3 in sALCL, including activating sequence variants in JAK1 / STAT3 (in approximately 20-30% of cases) and translocations involving ROS1 and TYK2 (BLOMBERY & al [30]; CRESCENZO & al [31]). Although STAT3 Ser614Arg mutations, as well as DNA binding (STAT3 His410Arg) have been observed, the explanation for the predilection of JAK / STAT3 activation in BIA-ALCL by STAT3 activation mutations is unclear, the genomic mechanism by which this aberration signalling seems to be different (BLOMBERY & al [30]). There were also observed mutations on the TP53 gene in patients who had been breast cancer treated and had breast implant reconstruction, plus a history of familial breast cancer (BLOMBERY & al [30]; AJORE & al [32]). TP53 gene mutations can also lead to Li-Fraumeni syndrome, which is a syndrome of multiple cancers predisposed to young age (very common before 30 years). The most common forms of cancer that occur in Li Fraumeni syndrome are osteosarcoma (bone cancer), breast cancer, soft-tissue sarcoma, acute leukemia, brain cancer, and adenocortical carcinoma. Recently a case was reported in which BIA-ALCL was associated with Li-Fraumeni syndrome, although only about 500 cases of Li-Fraumeni syndrome are known in the world (PASTORELLO & al [33]). Cases reported with this genetic anomaly are very few, and until now, a direct link between this mutation and the presence of the implant could not be achieved. It has also been demonstrated that most cases of ALK-negative lymphomas sALCL do not express a T-cell receptor, despite having rearranged TRG and TRB sites, which also appears to be counterbalanced in BIA-ALCL (BONZHEIM & al [34]; M. SHUGAY & al [35]). As a brief conclusion on the genetic determinism of BIA-ALCL, we can say that the aberrant signalling pathways in BIA-ALCL are similar to those in sALCL including abnormalities of the TP53, MYC and JAK / STAT3 models, and are characterized by a high recurrence in activation STAT3 mutations and recurrent deletions of 1p22 involving RPL5 (which have not been identified in sALCL at date); genetic alterations of the anomalies of TGF-β, PKC, Wnt / β-catenin, MYC, P2RX7, TMEM119 as well as high-level amplification of TNFRSF11A and PDGFRα (BLOMBERY & al [30]; FANCELLO & al [36]).

An exciting and consistent feature of BIA-ALCLs is their complex cytogenetics. This suggests that genomic instability may play a role in the formation or progression of tumours. For example, the genetic mutation on chromosome 17 induces the disruption of the P53 gene located on chromosome 17 (17p13.1), which results in increased tumour aggression (MULLER & al [37]). Human P53 plays an important role in apoptosis, genomic stability and inhibition of angiogenesis (WADE & al [38]; NWABUDIKE & al [39]). Another etiopathogenic model may be that one described related to altered epigenetic pathways and cell cycle dysregulation in healthy appearing skin of patients with koebnerized squamous cell carcinomas following skin surgery, “Table 1”.

### Table 1. Tumor cells in vivo cytogenetic evolution. Modified and adapted after GERORGIE & al [40].

| Cell Source | Clonal Cytogenetic Abnormalities |
|-------------|---------------------------------|
| Tumor cells from seroma fluid | dup(X)(q11q28), +1, del(1)(q32), i(1)(q10), add(3)(p11), der(3)(t(2,3)(p12,q26)), +6, der(6)(q6,6)(q12,q21.3)x2, add(8)(q11.2), add(11)(q23), add(14)(p11.1), -15, -17, -20, 80-91, idem (cp2) |
| Cells from lymph node | 34, XX [1]* |
| | +1, del(1)(q32)x2, +2, -3, der(3)(t(2,3)(p12,q26)), +6, der(6)(q6,6)(q12,q21.3)x2, add(9)(p22), -10, -12, -13, -14, -15, add(15)(p11.2), -16, add(16)(q11.2), -17, -18, -20, -20, -21, -21, -22 [1] |
| | 78-79, XX (cp3)* |
| | +X, +X, +1, +1, del(1)(q32)x2, i(1)(q10), +2, add(3)(p11), add(4)(q21), +6, +6 der(6)(q6,6)(q12,q21.3)x2, -8, add(9)(p22)x1-3, -10, add(10)(p13), add(11)(q23), +14, -15, add(15)(p11.2), +16, add(16)(q11.2)x2, -17, -17, -18, +19, -20, -22, i(22)(q10), +mar1-2 |
| | 46, XX [16] |

George E.V. et al. studied and correlated several tumour factors in BIA-ALCL: CD30, Ki67, CD8, CD15, CD45, CD25, CD20, TP53. It found that the combination of CD30 with strongly positive Ki67 suggests an increased proliferative index, while CD15 positivity was increased in the recurrent tumour, suggesting that CD15 may mark a more aggressive sub-clone of the basal tumour (GEROGIE & al [40]). Another possible contributing cause would be textured implants. Considered to be more stable and with a much lower rotation risk, textured implants were used with predilection. However, most of the BIA-ALCL cases appeared on textured implants, “Table 2” (LOCH-WILKINSON & al [18]; GEROGIE & al [40]).
Table 2. Aggressive cases of BIA-ALCL: Int., interval, Rt, right, Lt, left, BI, breast implant, CA, carcinoma, LN, lymph node, LAD, lymphadenopathy, LyP, lymphomatoid papulosis, CPT, capsulotomy, RT, radiation therapy, CT, chemotherapy, ASCT, autologous stem cell transplantation, CHOP, PBC, primary biliary cirrhosis, ALK-, anaplastic lymphoma kinase gene rearrangement negative (GERORGE & al [40]).

| Case/Ref. | Age/Int. at ALCL, PMH | Textured BI filled with | Presentation/Sites of disease | Markers | Genetics/ALK Status | Treatment/Outcome |
|-----------|-----------------------|-------------------------|-------------------------------|---------|---------------------|-------------------|
| Albeid et al. 2009 | 68/16, history of Rt breast ducal CA and PBC | silicone | Rt axillary LAD/Rt axillary Ns, Rt BI capsule, Lt axillary Ns | CD30+, CD45++, CD15+, CD2+, CD44+, EMA+, MUM1+ | Complex ALK- | CPT, 6 cycles CHOP/No known relapse |
| Carty et al. 2011 | 57/32, multiple BI revisions due to capsular contraction and implant rupture | silicone | B-symptoms, Lt axillary LAD/Lt BI capsule with chest wall invasion and pleural thickening | CD30+, CD4+ | Complex ALK- | CPT, RT, 5 cycles CHOP, salvage CT, ASCT/ Death from progressive disease 3 yrs after diagnosis |
| Gaudet et al. 2002 | 50/10, Lt breast CA, remote history of HL | Silicone | Mass overlying Rt BI/Dermal involvement overlying Rt BI | CD30+, CD2+, LCA+, weakly positive for CD3, CD5, CD43 | Complex ALK- | CHOP/Relapse 1 year later with pleural and pericardial effusions, mediastinal LAD, Unknown current status |
| Aladily et al. 2012 | 63/6+1, L breast CA, 3 yr history of LyP | saline | Effusion & mass in Rt breast/Rt breast | CD30+, CD3+, CD44+, CD2+, CD43+ | Complex ALK- | CPT/Died at 12 yrs post ALCL diagnosis |
| Aladily et al. | 47/9, breast CA | saline | Rt BI mass/Rt breast with effusion | CD30+, CD45+, CD43+, CD4+, EMA+, Granzyne B | Complex ALK1+ | CPT, RT, CT/ Died at 2 yrs post ALCL diagnosis |
| George E.V. | 67/8, breast CA | Silicone | Enlargement and Effusion in Rt breast/Rt breast | CD30+, CD15+, CD25+, CD6+, | Complex with genetic evolution ALK- | CPT at diagnosis, CHOP/ Etoposide at relapse. Patient is well without detectable disease |

In 2017, the FDA reported that of 231 cases of BIA-ALCL, 203 were on textured implants and only 28 on smooth implants (BERLIN & al [41]). On the other hand, in the structure of the silicone gel in the implants, many chemicals, such as vinyl derivatives, aromatic hydrocarbons (benzene, xyozol) and traces of metals. Some of these substances can cross the implant capsule and reach the tissues around the implant causing a chronic inflammation and implicitly an increased T lymphocyte influx, which may theoretically favour a BIA-ALCL (C. HILLARD & al [42]). Moreover, on an existing chronic inflammation, aromatic hydrocarbons can cause cytoplasmic and aryl hydrocarbon transcription factor activation (AHR) activation to turn cytochrome P450 transformation (CYP1Aa / 2 and 1B1 enzymes), the latter resulting in mutagenic DNA changes (ANDERSON & al [43]) also explained by the Wolf phenomenon (TATU & al [44]) but, on the other hand, AHR exhibits high levels in most forms of BIA-ALCL (KOLLURI & al [45]), and the bacteria attach much more easily to textured implants than the smooth ones, which would explain the higher incidence of BIA-ALCL on textured implants.

2. Diagnosis

BIA-ALCL is one of the 4 types of ALCL. All of these ALCL forms are positive for CD 30, but the clinical prognosis and prognosis is different, with BIA-ALCL having a rare evolution that can lead to death. BIA-ALCL is characterized by elevated levels of CD30, even in the absence of anaplastic lymphoma kinase (ALK) (FERRUFINO-SCHMIDT & al [46]).

From a clinical point of view, in most cases, it is manifested by the appearance of a periprosthetic serum with thickening of the capsule and signs of capsular contraction. The average occurrence interval is 7-8 years after implant insertion (CLEMENS & al [47]). Can also present chronic breast dermatitis, breast deformities and axillary adenopathies. A minimal number of cases have been reported in the absence of a collection of peri-prostheses in combination with a severe capsular contraction, a mass or a nodule. BIA-ALCL can also occur bilaterally, although this can occur even less frequently. The axillary invasion of the lymph nodes is quite frequent, according to some authors, reaching 93%, with the invasion of internal and supraclavicular mammary lymph nodes (FERRUFINO-SCHMIDT & al [46]). Very rarely, it can manifest itself as a solid capsular tumour (J. Xu & al [48]).

From para-clinical investigations, any serum starting more than 1 year associated with an implant should be investigated by mammary and axillary ultrasonography and by highlighting the structure of the thoracic wall, as it shows in “Figure 2”. The sensitivity of ultrasound for detecting a BIA-ALCL is estimated to be 84% for serum and 46% for solid tumours. The specificity of ultrasound for detection of a BIA-ALCL is estimated to be 75% for serum and 100% for solid tumours (ADRADA & al [49]). If mammary echography is inconclusive, the next step is to perform, magnetic resonance imaging (MRI). Positron emission tomography-computed tomography (PET / CT) may also be an option in the diagnosis of advanced BIA-ALCL, especially in the detection of metastasis or invasion of the thoracic wall, it is also a postoperative follow-up method, but at least 3 months after surgery (BRODY & al [50]).

Sensitivity/specificity for serum:
- Ultrasound: 84 / 75%
- Computer tomography (CT): 55 / 83%
- MRI: 82 / 33%
- PET-CT: 38 / 83%
Sensitivity/specificity for solid tumours:
- Ultrasound: 46/100%
- CT: 50/100%
- MRI: 82/33%
- PET-CT: 64/88%

Mammography is inferior to breast ultrasound and MRI, both as sensitivity and specificity, without being able to differentiate solid tumor serum [73/50%] [49]. These investigations raise the suspicion of a BIA-ALCL, but the diagnosis of certainty is supported by the exogeneous aspiration of the periprosthetic fluid with cytology and immunohistochemistry for CD30 and ALK. In the case of patients with axillary adenopathies or chronic dermatitis, the biopsy with the histopathological and immunohistochemical examination is indicated for CD30 and ALK (CLEMENS & al [51]). Since the implant capsule drains through various lymphatic tracts and to various lymph nodes, it is not recommended to make the sentinel ganglion. Only lightened lymph nodes detected by palpation will be excised.

The differential diagnosis of a seroma within one year old includes infection, trauma, hematoma, implant rupture, double capsule, synovial metaplasia, breast cancer and idiopathic causes. Differential diagnosis with other breast malignancies may require other tumour markers such as CD2, CD3, CD4, CD5, CD7, CD8, CD45 and anaplastic lymphoma kinase (ALK), BIA-ALCL is always ALK-negative (QUESADA & al [52]).

### 3. Treatment

Treatment of BIA-ALCL depends on the clinical stage of the disease, and the National Comprehensive Cancer Network proposed a very comprehensive algorithm, “Figure 3”.

Non-Hodgkin’s lymphomas are classified most frequently according to the staging of Ann Arbor, modified by Lugano. According to this classification, stage IE is defined by the invasion of a single extranodal site (E), such as the implant capsule, while stage IIE appears to spread to nearby tissues or local lymph nodes invasion (B.D. CHESON & al [53]). Thus, if we follow this classification, almost all BIA-ALCLs are diagnosed at an early stage, either in stage IE (83-84%) or stage IIE (10-16%), while in advanced stages only 0-7% of cases are diagnosed (CLEMENS & al [21]). This classification does not take into account the capsular invasion in BIA-ALCL, which makes it less usable in this form of lymphoma, which is why NCCN adopted the TNM classification of BIA-ALCL, and we revealed in “Table 3”.

### Table 3. TNM Classification by NCCN guidelines (2019). (CLEMENS & al [51])

| TNM Classification | TNM Stage |
|--------------------|-----------|
| T: Tumour extent   | IA T1N0M0 |
| T1                 | IB T2N0M0 |
| T2                 | IC T3N0M0 |
| T3                 | IA T4N0M0 |
| T4                 | IIB T1-T3N1M0 |
| N: Lymph node      | III T4N1-N2M0 |
| N0                 | IV T any, N any, M1 |
| N1                 | One regional lymph node |
| N2                 | Multiple regional lymph nodes |
| M: Metastasis      | M0 No distant spread |
| M1                 | M1 Spread to other organs/distant sites |

Compared to the Ann Arbor classification, TNM classification more precisely divides the disease into clinical stages, thus allowing a more accurate assessment of the therapeutic protocol and prognosis. Thus, according to some authors, the incidence of BIA-ALCL depending on the TNM stages would be: 35-70% stage I, 11% stage IB, 8-13% stage IIC, 8-25% stage IIA, 3-5% in Stage IIB, 3-9% in Stage III and only 1-2% in Stage IV (ADRADA & al [49]; DOREN & al [5]). Thus, BIA-ALCL treatment is performed according to the TNM classification.

In stage 1-3, complete removal of the implant and the surrounding fibrous capsule is sufficient to eradicate
the disease (see figure 3). In advanced stages, it is necessary to associate chemotherapy or extended surgical excisions, and very rarely the association of radiotherapy (Figure 3). At present, the role of radical mastectomy or sentinel ganglion is not clearly defined. Complete axillary dissection was rarely used in cases where more lymph nodes were invasive. The JAK / STAT3 targeted tyrosine kinase inhibitor may be a possible treatment for infiltrative BIA-ALCL (CHIARLE & al [54]). It is estimated that 2-4% develop bilateral disease, requiring treatment for both breasts.

![Figure 3. Treatment of BIA-ALL. Modified and adapted after NCCN (CLEMENS & al [51]). Breast implant-associated anaplastic large cell lymphoma disease algorithm.](image)

Current evidence-based algorithm for achieving diagnosis followed by treatment by stage of the disease. Bx, biopsy, CBC, complete blood count, CHOP, cyclophosphamide doxorubicin vincristine prednisolone. CMP, complete metabolic profile, daE, dose-adjusted etoposide, FNA, fine needle aspiration, LDH, lactate dehydrogenase, MRI, magnetic resonance imaging, PET/CT, positron emission tomography-computed tomography, RT, radiation therapy.

Radiotherapy is occasionally indicated when the excision margins are positive, non-resectable tumour, chest wall invasion or relapse, with the usual doses being 24-36 Gy (CLEMENS & al [19]).

Chemotherapy is indicated in the following cases: non-resectable tumours, tumours that have spread to the breast parenchyma or chest wall, axillary lymph node invasion. Chemotherapy is performed according to the CHOP regimen, with different rates of success. In CHOP-resistant patients, Brentuximab Vedotin, which is made up of anti-CD30 monoclonal antibodies, is used as a neo-adjuvant, with encouraging BIA-ALCL results in advanced stages (ALDERUCCIO & al [55]). Advani claims that following this treatment with Brentuximab Vedotin, the response rate was 86% and the complete remission rate of 59% (B. PRO & al [56]). Systemic therapy is warranted in patients in stage II-IV Lugano or the stage IB-IV TNM, ALK-negative lymphomas respond less well to CHOP than ALK-positive (survival rates of 5 to 40% versus 70-90%) (HAPGOOD & al [57]). After Clemen, about two-thirds of patients with BIA-ALCL showed tumor progression after CHOP (CLEMENS & al [20]). Patients who did not respond to baseline chemotherapy had a complete response to Brentuximab, but other chemotherapies but very rare chemotherapy protocols were used: ABVD (Adriamycin, Bleomycin, vinblastine, dacarbazine), hyper-CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with methotrexate and cytarabine), and ICE (ifosfamide, carboplatin, etoposide) (CLEMENS & al [21]; LEBERFINGER & al [58]; SHAH & al [59]; MAZILU [60]).

The overall survival rate for patients diagnosed with BIA-ALCL is 89% at five years and is dependent on the stage in which the disease is diagnosed.

The relapse rate after surgical excision is 14.3% for T4 patients and 0% for patients in T1-T3 stages (CLEMENS & al [21]). Local relapse is due to the incomplete resection of the implant capsule.

There is also the possibility, reduced what is right, spontaneous remission of the disease, Fleming reporting in 2018, 2 spontaneous regression of BIA-ALCL (FLEMIN& al [61]).

There are currently 4 cases reported by BIA-ALCL to transgender. Of these, 3 patients were Ann Arbor IE and treated with full surgical resection and CHOP adjuvant chemotherapy, a 4th case was diagnosed in Stage IE (TNM Stage III) and was treated with CHOP chemotherapy (4 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone), radiotherapy (3600 cGy in 180 cGy fractions) and surgical excision. (DE BOER & al [62]; PATZELT & al [63]; ALI & al [64]; CIUHU & al [65]). They all had textured implants.

Postoperative surveillance will be done through 6-month clinical follow-up and 2-year breast ultrasound for 5 years (ARDELEANU & al [66]).

In 2019, the National Comprehensive Cancer Network (NCCN) has updated the Consensus Guidelines on the Diagnosis and Treatment of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL), which is the gold standard in diagnosing and treating BIA-ALCL. This guide addresses the disease in its function and is recognized by the FDA. Observing this guide assists patients with the most modern and optimal treatment, this guideline based on the latest and most complex studies in the world. (BERETTA & al [67]; DI VIRGILIO & al [68]; PANTEA STOIAN& al [69]; ROUANET & al [70]).

Exceptionally, differential diagnosis can also be made with solid tumors such as lipomatosis (ARDELEANU & al [71]), case of course the treatment and prognosis is totally different. Certainly certain diagnostic techniques used today in other forms of cancer will be extrapolated.
to BIA-ALCL (ARDELEANU & al [72]; CALOTÁ & al [73]; OZEN & al [74]).

**Conclusion**

The appearance of high-cell anaplastic lymphoma in patients with mammary implants is a topical issue, with more than 1.7 million implants being mounted in the world and over 500 cases of BIA-ALCL reported, of which 16 deaths. The estimated incidence of the disease is 2.03 to 1 million people or 1 in 30,000 women with mammary implants. The average duration of implant exposure varies on average from 7 to 13 years.

The causes of BIA-ALCL are still incompletely elucidated. Several possible etiologies such as chronic inflammations/infections, textured implants, host allergenic terrain, genetic determinism for haematological cancers, genetic mutations, removal of implants toxins are incriminated.

Clinically, it is most often manifested by the appearance of a massive serum that appeared on the average after 7-8 of the implant, most often unilaterally, accompanied or not by other signs such as skin pruritus.

The diagnosis of certainty is supported by the tumour marker CD30 and ALK, which is harmful.

Treatement varies depending on stages. For incipient stages (I–II), implant removal and capsule excision are sufficient, while chemotherapy or radiotherapy is required for advanced or invasive stages. The most commonly used chemotherapy regimen is CHOP (cyclophosphamide doxorubicin vincristine prednisolone).

The gold standard in diagnosing and treating BIA-ALCL is the NCCN guide of 2019.

The differential diagnosis of a seroma within 1 year old includes infection, trauma, hematoma, implant rupture, double capsule, synovial metaplasia, breast cancer and idiopathic causes.

Prognosis is a good one if the disease is treated in the early stages and can become less favourable in advanced stages. The relapse rate after surgical excision is 14.3% for T4 patients and 0% for patients in T1-T3 stages. Local relapse is due to the incomplete resection of the implant capsule. There are also reports of spontaneous remission.

Due to the increasing incidence of BIA ALCL simultaneously with the increase in the number of breast augmentations with implant throughout the world but also our country, we consider very importantly, on the one hand, the knowledge by all plastic surgeons of the manifestations of this disease as well as the diagnosis and the proper treatment, but also the creation of a unique register of breast augmentations. There remains an open discussion on the type of implant chosen, smooth or textured, yet there are no definite conclusions in this regard, as there have been reported cases of BIA-ALCL on both textured and smooth implants. In November 2019, the first case of BIA-ALCL was diagnosed in Romania with a patient with Allergan Natrelle Inspira implants in dual-plane technique, and implants mounted 5 years ago.

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**Conflicts of Interest**

The authors declare no conflict of interest.

**References**

1. R.N. AL-ROHIL, C.A. TORRES-CABALA, A. PATEL, et al. Loss of CD30 expression after treatment with brentuximab vedotin in a patient with anaplastic large cell lymphoma: a novel finding. *Journal of Cutaneous Pathology*, 43(12):1161-1166 (2016).

2. M. BIZIAC, C. SELMI, S. PRAPROTNIK et al. Silicone implants and lymphoma: the role of inflammation. *Journal of Autoimmunity*, 2015, 65: 64-73.

3. J. KRICHENDORFF, E.M. FALLENBERG, K. SOLBACH, C. GERBER-SCHÄFER, C. RANCSŐ, U. VON FRITSCHEN. Uwe von Fritschen. Breast Implant-Associated Lymphoma. Deutsches Ärzteblatt International. *Dscht Arztebl Int*, 115:628-635 (2018).

4. S.K. STORY, M.K. SCHOWALTER, L.J. GESKIN. Breast implant-associated ALCL: a unique entity in the spectrum of CD30+ lymphoproliferative disorders. *Oncologist*, 18(3): 301-307 (9) (2013).

5. E.L. DOREN, R.N. MIRANDA, J.C. SELBER, P.B. GARVEY, J. LIU, L.J. MEDEIROS, C.E. BUTLER, M.W. CLEMENS. U.S. Epidemiology of breast implant-associated anaplastic large cell lymphoma. *Plast. Reconstr. Surg.*, 139:1042-1050 (2017).

6. J.R. KEECH, B.J. CREECH. Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant. *Plastic and Reconstructive Surgery*, 100(2):554-555 (1997).

7. S.H. SWERDLOW, E. CAMPO, S.A. PILERI et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*, 127(20): 2375-2390 (2016).

8. D. CHIIHARA, M.A. FANALE. Management of Anaplastic Large Cell Lymphoma. *Hematology/Oncology Clinics of North America*, 31(2):209-222 (2017).

9. The Non-Hodgkin’s Lymphoma Classification Project, A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin’s lymphoma. *Blood*, 89(11):3909-3918 (1997).

10. I. KAARTINEN, K. SUNELA, J. ALANKO, K. HUKKINEN, M.L. KARJALAINEN-LINDSBERG, C. SVARVAR. Breast implant associated anaplastic large cell lymphoma – from diagnosis to treatment. *Eur. J. Surg. Oncol.*, 43:1385-1392 (2017).

11. S.H. SWERDLOW, World Health Organization, International Agency for Research on Cancer. 2017 WHO classification of tumours of hematopoietic and lymphoid tissue, 4th ed. Lyon, France: IARC (2017).

12. Administration UFaD. Breast implant associated anaplastic large cell lymphoma (BIA-ALCL), (2017).

13. L. JOHNSON, et al. Breast implant associated anaplastic large cell lymphoma: the UK experience. Recommendations on its management and implications for informed consent. *Eur. J. Surg. Oncol.*, 43:1393-1401 (2017).

14. A. CAMPANALE, R. BOLDRINI. BIA-ALCL incidence: the variable to be included in the denominator. *Plast. Reconstr. Surg.*, 141(5):1 (2018).

15. M. De BOER, F.E. van LEEUWEN, M. HAUPTMANN et al. Breast implants and the risk of anaplastic large-cell lymphoma in the breast. *JAMA Oncol.*, 4:335-341 (2018).
16. C. LAURENT, A. DELAS, P. GAULARD et al. Breast implant-associated anaplastic large cell lymphoma: two distinct clinicopathological subtypes with different outcomes. Ann. Oncol., 27:306–314 (2016).

17. BfArM. 2018 See http://www.bfarm.de/SharedDocs/Risikoinformationen/DE/Brustimplantate/ALCL_FDA.html

18. A. LOCH-WILKINSON, K.J. BEATH, R.J.W. KNIGHT et al. Breast implant associated anaplastic large cell lymphoma in Australia and New Zealand: high-surface area textured implants are associated with increased risk. Reconstr. Surg., 140:645-654 (2017).

19. M.W. CLEMENTS, S.M. HORWITZ. NCCN consensus guidelines for the diagnosis and management of breast implant associated anaplastic large cell lymphoma. Aesthet Surg J, 37(3):285-289 (2017).

20. M.W. CLEMENTS, G.S. BRODY, R.C. MAHABIR, R.N. MIRANDA. How to diagnose and treat breast implant-associated anaplastic large cell lymphoma. Plast Reconstr Surg., 141(4):586e-599e (2018).

21. M.W. CLEMENTS, L.J. MEDEIROS, C.E. BUTLER et al. Complete surgical excision is essential for the management of patients with breast implant-associated anaplastic large cell lymphoma. J Clin Oncol, 34(2):160-168 (2016).

22. M.Q. DU. MALT lymphoma: genetic abnormalities, immunological stimulation and molecular mechanism. Best Pract. Res. Clin. Haematol, 30:13-23 (2017).

23. W.P. ADAMS, E.J. CULBERTSON, A.K. DEVIA, M. MAGNUSSON et al. Macrotextured breast implants with defined steps to minimize bacterial contamination around the device: experience in 42 000 implants. Plast. Reconstr. Surg., 140:427-431 (2017).

24. T.J. STEWART, M.J. SMYTH Improving cancer immunotherapy by targeting tumor-induced immune suppression. Cancer Metastasis Rev., 30:125-140 (2011).

25. M.E. KADIN, A. DEVIA, H. XU, J. MORGAN: Biomarkers Provide Clues to Early Events in the Pathogenesis of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Aesthet. Surg. J., 36:773-781 (2016).

26. H. HU, K. JOHANI, A. ALMATROUDI, K. VICKERY et al. Bacterial biofilm infection detected in breast implant-associated anaplastic large-cell lymphoma. Plast. Reconstr. Surg.,137:1659-1669 (2016).

27. M.Y. WANG, C. CHEN, X.Z. GAO, J. LI et al. Distribution of Helicobacter pylori virulence markers in patients with gastroduodenal diseases in a region at high risk of gastric cancer. Microb. Pathog., 59:60-13-18 (2013).

28. F. FITZAL, S.D. TURNER, L. KENNER. Is breast implant-associated anaplastic large cell lymphoma a hazard of breast implant surgery?. Open Biol., 9(4): 190006 (2019).

29. M.E. KADIN, J. MORGAN, H. XU, A.L. EPSTEIN et al. IL-13 is produced by tumor cells in breast implant-associated anaplastic large cell lymphoma: implications for pathogenesis. Hum. Pathol., 78:54–62 (2018).

30. P. BLOMBERY, E. THOMPSON, G.L. RYLAND, R. JOYCE et al. Frequent activating STAT3 mutations and novel recurrent genomic aberrations detected in breast implant-associated anaplastic large cell lymphoma. Oncotarget, 9(90):36126-36136 (2018).

31. R. CRESCENZO, F. ABATE, E. LASORSA, F. TABBO, F. et al. Convergent mutations and kinase fusions lead to oncogenic STAT3 activation in anaplastic large cell lymphoma. Cancer Cell, 27:516-532 (2015).

32. R. AJORE, D. RAISER, M. MCCONKEY, M. JOUD et al. Deletion of ribosomal protein genes is a common vulnerability in human cancer, especially in concert with TP53 mutations. EMBO Mol Med., 9:498-507 (2017).

33. R.G. PASTORELLO, F. D’ALMEIDA COSTA, C.A.B.T. OSÓRIO, F.B.A. MAKDISSI, et al. Breast implant-associated anaplastic large cell lymphoma in a Li-FRAUMENI patient: a case report. Diagnostic Pathology, 13(1):10 (2018).

34. IRINA BONZHEIM, EVA GEISSINGER, SABINE ROTH, ANDREAS ZETTL, ALEXANDER MARX, ANDREAS ROSENWALD, HANS KONRAD MÜLLER-HERMLE-LINK, THOMAS RÜDIGER. Anaplastic large cell lymphomas lack the expression of T-cell receptor molecules or molecules of proximal T-cell receptor signalling. Blood, 104:3358-3360 (2004).

35. M. SHUGAY, D.V. BAGAEV, I.V. ZVYAGIN, R.M. VROOMANS et al. VDJdb: a curated database of T-cell receptor sequences with known antigen specificity. Nucleic Acids. Res., 46(D1):D419–D27 (2018).

36. L. FANCELLO, K.R. KAMPEN, I.J. HOFMAN, J. VERBEEK et al. The ribosomal protein gene RPL5 is a haplo insufficient tumor suppressor in multiple cancer types. Oncotarget, 8:14462–14478 (2017).

37. P.A. MÜLLER, K.H. VOUSDEN. p53 mutations in cancer. Nat Cell Biol., 15:2-8 (2013).

38. M. WADE, Y.C. LI, G.M. WAHL. MDM2, MDMX and p53 in oncogenesis and cancer therapy, Nat Rev Cancer,13, 83-96 (2012).

39. L.C. NWABUDIKE, A.L. TATU, A.L. REPLY TO GAMBICHLER T et al. Altered epigenetic pathways and cell cycle dysregulation in healthy appearing skin of patients with koebnerized squamous cell carcinomas following skin surgery. J Eur Acad Dermatol Venereol, 33(1):e3-e4 (2019).

40. E.V. GEORGE, J. PHARM, C. HOUSTON, S. ALQUAN et al. Breast implant-associated ALK-negative anaplastic large cell lymphoma: a case report and discussion of possible pathogenesis. Int J Clin Exp Pathol, 6(8):1631-1642 (2013).

41. E. BERLIN, S. KUNWAR, M. CHRISTOPHER, S. ILAN et al. Breast implant-Associated Anaplastic Large Cell Lymphoma: Case Report and Review of the Literature. Case Reports in Hematology. Article ID 2414278 (2018).

42. C. HILLARD, J.D. FOWLER, R. BARTA, B. CUNNINGHAM, B. Silicone breast implant rupture: a review. Gland Surg, 6:163-168 (2017).

43. G.D. ANDERSON, L.N. CHAN. Pharmacokinetic drug interactions with tobacco, cannabinoids and smoking cessation products. Clin Pharmacokinet, 55:1353-1368 (2016).

44. A.L. TATU, L.C. NWABUDIKE. Reply to Happle R. And al. Koebner’s sheep in Wolf’s clothing: does the isotopic response exist as a distinct phenomenon? J Eur Acad Dermatol Venereol, 32(8):e336-337 (2018).

45. S.K. KOLLURI, U.H. JIN, S. SAFE. Role of the aryl hydrocarbon receptor in carcinogenesis and potential as an anti-cancer drug target. Arch. Toxicol, 91:2497-2513 (2017).

46. M.C. FERRUFINO-SCHMIDT, L.J. MEDEIROS, H. LIU, M.W. CLEMENTS et al. Clinicopathologic features and prognostic impact of lymph node involvement in patients with breast implant associated anaplastic large cell lymphoma. Am. J. Surg. Pathol., 42: 293-305 (2018).

47. M.W. CLEMENTS, R.N. MIRANDA. Coming of age: breast implant-associated anaplastic large cell lymphoma after 18 years of investigation. Clin. Plast. Surg., 42:605-613 (2018).
48. J. XU, S. WEL. Breast implant-associated anaplastic large cell lymphoma: review of a distinct clinicopathologic entity. Arch.Path.Lab.Med, 138(6):842-846 (2014).
49. B.E. ADRADA, R.N. MIRANDA, G.M. RAUCH et al. Breast implant associated anaplastic large cell lymphoma: sensitivity, specificity, and findings of imaging studies in 44 patients. Breast Cancer Res Treat, 147(1):1-14 (2014).
50. G.S. BRODY, D. DEAPEN, C.R. TAYLOR, C.R. et al. Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases. Plast Reconstr Surg, 135(3):695-705 (2015).
51. M.W. CLEMENS, E.D. JACOBSEN, S.M. HORWITZ. 2019 NCCN consensus guidelines on the diagnosis and treatment of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL). Aesthet Surg J, 39(Suppl. 1): S3–S13 (2016).
52. A.E. QUESADA, L.J. MEDEIROS, M.W. CLEMENS, M.C. FERRUFINO-SCHMIDT et al. Breast implant-associated anaplastic large cell lymphoma: a review. Mod Pathol, 32:166-188 (2019).
53. B.D. CHESON, R.I. FISHER, S.F. BARRINGTON et al. Alliance, Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell. Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Osea; German High-Grade Lymphoma Study Group; German Hodgkin’s Study Group; Japanese Lymphoma Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol, 32(27):3059-3068 (2014).
54. R. CHIARLE, W.J. SIMMONS, H. CAI, G. DHALL et al. Stat3 is required for ALK-mediated lymphomagenesis and provides a possible therapeutic target. Nat Med, 11:623-629 (2005).
55. J.P. ALDERUCCIO, A. DESAI, M.M. YEPES, J.R. CHAPMAN et al. Frontline brentuximab vedotin in breast implant-associated anaplastic large-cell lymphoma. Clin Case Rep, 6:634-636 (2018).
56. B. PRO, R. ADVANI, P. BRICE et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large cell lymphoma: results of a phase II study. J Clin Oncol, 30:2190-2196 (2012).
57. G. HAPGOOD, K.J. SAVAGE. The biology and management of systemic a
58. naplastic large cell lymphoma. Blood, 126:17-25 (2015).
59. A.N. LEBERFINGER, B.J. BEHAR, N.C. WILLIAMS et al. Breast implant-associated anaplastic large cell lymphoma: a systematic review. JAMA Surg, 152(12): 1161-1168 (2017).
60. M.N. SHAH, M.W. CLEMENS, S.M. HORWITZ. How I treat breast implant-associated anaplastic large cell lymphoma. Blood, 132(18):1889-1898 (2018).
61. L. MAZILU, D.L. STANCULEANU, A.D. GHEORGHE et al. Incidence of chemotherapy-induced peripheral neuropathy in cancer patients in clinical practice. Farmacia, 67(3):472-476 (2019).
62. D. FLEMING, J. STONE, P. TANSLEY. Spontaneous Regression and Resolution of Breast Implant-Associated Anaplastic Large Cell Lymphoma: Implications for Research, Diagnosis and Clinical Management. Aest Plast Surg, 42:672-678 (2018).
63. M. DE BOER, W.B. VAN DER SLUIS, J.P. DE BOER et al. Breast implant associated anaplastic large-cell lymphoma in a transgender woman. Aesthet Surg J, 37:83-87 (2017).
64. M. PATZELT, L. ZARUVOBA, P. KLENER et al. Anaplastic large-cell lymphoma associated with breast implants: a case report of a transgender female. Aesthetic Plast Surg, 42:451-455 (2018).
65. N. ALI, K. SINDHU, R.L.A. BAKST. A Rare Case of a Transgender Female With Breast Implant–Associated Anaplastic Large Cell Lymphoma Treated With Radiotherapy and a Review of the Literature. Journal of Investigative Medicine High Impact Case Reports, 7:1-5 (2019).
66. A.N. CIUHU, A.M. PANTEA-STOIAN, C. NITIPIR et al. Assessment of cachexia in cancer patients with advanced disease. Conference: 3rd International Conference on Interdisciplinary Management of Diabetes Mellitus and its Complications (INTERDIAB) Location: Bucharest, ROMANIA Date: MAR 02-04, 2017.Sponsor(s): Assoc Renal Metab & Nutrit Studies; AstraZeneca Diabetes; MSD Diabetes; novo nordisk; SANOFI INTERDIAB 2017: DIABETES MELLITS IN INTERNAL MEDICINE Book Series: International Conference on Interdisciplinary Management of Diabetes Mellitus and its Complications, 139-147 (2017).
67. V. ARDELEANU, C. GEORGESCU, L.D. FRÎNCU et al. Angiogenesis as Prospective Molecular Biology Technique for Cancer Study. Romanian Biotechnological Letters, 19(5): 9637-9648 (2014).
68. G. BERETTA, A. RICHARDS, M. MALACCO, M. J. Chemical and biochemical composition of late periprosthetic fluids from women after explantation of ruptured Poly Implant Prothese (PIP) breast prostheses. Pharm. Biomed. Anal, 84:159-167 (2013).
69. F. DI VIRGILIO, D. DAL BEN, A.C. SARTI, A.C., L.L. GIULIANI et al. The P2X7. Immunity, 47:15-31 (2017).
70. A. PANTEA STOIAN, R. HAINAROSIE, C. PIETROSANU et al. Modern concepts in non-surgical esthetics; a review. Journal of Mind And Medical Sciences, 6(2):190-195 (2019).
71. P. ROUANET, J.M. FABRE, V. TICA, V. ANAF et al. Ann Plast Surg, 34(5):465-470 (1995).
72. V. ARDELEANU, G.R. CHEBAC, C. GEORGESCU, D. VESA et al. The modifications suffered by the peri-esophageal anatomical structures in the hialna hernia disease: a qualitative and quantitative microanatomic study. Romanian Journal of Morphology and Embryology, 51(4):765-770 (2010).
73. V. ARDELEANU, L.L. FRANCU, C. GEORGESCU. Neangiogenesis, assessment in esophageal adenocarcinomas. Indian J Surg, 77:971-976 (2014). DOI 10.1007/s12262-014-1091-9.
74. F. CALOTĂ, C. MEŞINĂ, S.S. MOGOANȚĂ, D. CALOTĂ. Oncogenesis- kaleidoscopic and multi-level reality. J Mind Med Sci, 6(1): 31-40 (2019). DOI: 10.22543/7674.62.P3140
75. V. OZEN, M.E. ORHAN. Review of the effects of anesthetic agents used as premedication for patients undergoing electroconvulsive therapy with diagnoses of bipolar disorder or major depression on convulsion, recovery period, and hemodynamic parameters. J Mind Med Sci, 6(2): 271-277 (2019). DOI: 10.22543/7674.62.P271277