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Breast implant associated anaplastic large cell lymphoma: proposal for a monitoring protocol

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Abstract:	Background Aim of the study was to report 4 cases of breast implant associated anaplastic large cell lymphoma (BIA-ALCL) from a single institution and to propose a multidisciplinary protocol. Methods From 2012-2014, four BIA-ALCL cases were diagnosed. The authors performed the original operation and no patients were referred to their practice. Case-1, -2, -4 were a CD4+/CD30+/ALK-ALCL with previous textured-implant reconstruction, while case-3 was a CD8+/CD30+/ALK-ALCL with previous polyurethane-implant augmentation. A retrospective study of all patients who underwent breast implant positioning was performed to identify any misdiagnosed cases. Results Of 483 patients, 226 underwent reconstruction with latissimus dorsi flap and prosthesis, 115 had skin/nipple-sparing mastectomy and prosthesis and 117 had expander/implant procedure while 25 underwent breast augmentation. Fifty-eight (12%) cases received implant replacement for capsular-contracture, 15 (3.1%) experienced late-onset seroma while 4 (0.83%) had both capsular-contracture and seroma. A total of 77 (16%) symptomatic patients received surgical revision (capsulectomy/capsulotomy) and/or seroma evacuation. The second look on histologic specimens did not identified misdiagnosed cases. Due to this retrospective study revealing different treatment approaches, a multidisciplinary protocol for suspected BIA-ALCL was established. Ultrasound and cytological examination are done in case

	of periprosthetic effusion. If BIA-ALCL is diagnosed, implant removal with capsulectomy is performed. If disseminated disease is detected through PET/TC total-body, patient is appointed to the oncology department. Conclusion Multidisciplinary protocol is mandatory for both early diagnosis and patient management. Until definitive data emerge regarding the exact etiopathogenesis of BIA-ALCL, our suggestion is to offer only autologous reconstruction if patients desire it.
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Abstract

Background

Aim of the study was to report 4 cases of breast implant associated anaplastic large cell lymphoma (BIA-ALCL) from a single institution and to propose a multidisciplinary protocol.

Methods

From 2012-2014, four BIA-ALCL cases were diagnosed. The authors performed the original operation and no patients were referred to their practice. Case-1, -2, -4 were a CD4+/CD30+/ALK- ALCL with previous textured-implant reconstruction, while case-3 was a CD8+/CD30+/ALK- ALCL with previous polyurethane-implant augmentation. A retrospective study of all patients who underwent breast implant positioning was performed to identify any misdiagnosed cases.

Results

Of 483 patients, 226 underwent reconstruction with latissimus dorsi flap and prosthesis, 115 had skin/nipple-sparing mastectomy and prosthesis and 117 had expander/implant procedure while 25 underwent breast augmentation. Fifty-eight (12%) cases received implant replacement for capsular-contracture, 15 (3.1%) experienced late-onset seroma while 4 (0.83%) had both capsular-contracture and seroma. A total of 77 (16%) symptomatic patients received surgical revision (capsulectomy/capsulotomy) and/or seroma evacuation. The second look on histologic specimens did not identified misdiagnosed cases. Due to this retrospective study revealing different treatment approaches, a multidisciplinary protocol for suspected BIA-ALCL was established. Ultrasound and cytological examination are done in case of periprosthetic effusion. If BIA-ALCL is diagnosed, implant removal with capsulectomy is performed. If disseminated disease is detected through PET/TC total-body, patient is appointed to the oncology department.

Conclusion

Multidisciplinary protocol is mandatory for both early diagnosis and patient management. Until definitive data emerge regarding the exact etiopathogenesis of BIA-ALCL, our suggestion is to offer only autologous reconstruction if patients desire it.

Clinical question/level of evidence: Risk, V

Text

Introduction

Breast implants have been routinely used for reconstructive and aesthetic purposes since 1962. In 1992, United States Food and Drug Administration (FDA) raised concerns on the connection between breast implants and the development of autoimmune diseases and/or cancer that were later dismissed by various studies.[1-4]

Breast cancer is the most frequent tumor affecting women (1.67 million new cancer cases diagnosed in 2012) and the leading cause of death among women between the age of 35 to 50.[5] Primary lymphoma of the breast is very rare and accounts only for 0.04-0.5% of all malignant breast tumors, 1-2% of extra-nodal lymphomas and < 1% of all non Hodgkin lymphomas.[6] Can either be primary breast neoplasm or part of a disseminated disease, being > 90% B cell lineage lymphomas, and < 10%, of T cell lineage and usually represented by peripheral T-cell lymphoma not otherwise specified (PTCL-NOS).[7] Only 6% of all T cell lineage lymphomas are diagnosed as anaplastic large cell lymphomas (ALCL).[7] Breast-implant associated ALCL (BIA-ALCL) is now widely accepted as a distinct and unique pathology and a great interest has been given to this topic by the medical and lay press because of the culprit involved and because the exact etiopathogenesis has not been clarified yet.[8,9] The FDA, on 26 January 2011, released an alert stating that women with breast implants have an increased, although very low, risk of developing BIA-ALCL.[10] Currently, in the published literature, there are 63 documented cases of primary BIA-ALCL. As research goes on to understand the exact etiopathogenesis, reporting all new cases is mandatory to estimate the statistic significance of its real incidence. We experienced four consecutive cases that lead to a retrospective study of all patients who underwent breast implant positioning at our institution to identify any

misdiagnosed cases. A protocol involving a multidisciplinary approach was established to better diagnose and manage patients with suspected symptomatology.

Material and Methods

Case 1

In September 2005, a 40-year-old woman had modified radical mastectomy (MRM) for lobular carcinoma of her left breast, axillary lymph node dissection and reconstruction with a BIOCELL® textured expander (Inamed 133 LV). She received 6 cycles of adjuvant chemotherapy. In January 2006, the expander was replaced with a BIOCELL® textured silicone gel-filled implant (Inamed 410LX 625 gr) and contralateral breast augmentation (a BIOCELL® textured silicone gel-filled implant, Inamed 410LX 255 gr) was performed for symmetrization. A thin fibrous capsule was found around the expander. In January 2011, during a routine bilateral breast ultrasound examination (UE) fine needle aspiration (FNA) of a small periprosthetic liquid was done on the left side showing numerous lymphocytes, histiocytes and polymorphonuclear neutrophils in a fibrinous base compatible with an inflammatory process. The patient was clinically asymptomatic and refused breast implant removal and histologic examination. In September 2012, a bilateral axillary UE showed numerous round lymph nodes with hypoechoic hilum and anarchic vascularity on the right side. Excisional biopsy of suspected right axillary lymph nodes was done. Histologic analysis showed the presence of large cells with abundant cytoplasm and a pleomorphic nucleus clustered together within the sinus of the lymph node. Immunohistochemistry stains revealed CD30+, CD4+, ALK-, CD45-, CD3-, CD15-, and cytokeratin negative cells confirming the diagnosis of BIA-ALCL (Figure 1). Bilateral breast implant removal was decided with complete capsulectomy. During surgery a small amount of left side seroma was identified and sent for histological, cytological and bacteriological examination. The periprosthetic capsule of the left side was characterized by infiltrations of ALCL that resulted CD30+, CD4+, ALK-, CD3-, CD8-, CD20- and

CD79a-, while the capsule of the right side was negative. Periprosthetic liquid of the left side was identified as a serous fluid filled with CD30+ cells with a large nucleus and abundant cytoplasm. Due to the positive right axillary lymph node the patient received 3 cycles of CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone) chemotherapy postoperatively that lead to complete remission. She had a Positron Emission Tomography (PET) and Computerized Tomography (CT) total-body scan that did not reveal any other suspected areas. The patient was disease-free at last follow-up in September 2014.

Case 2

In May 2008, a 49-year-old woman had MRM for recurrent ductal carcinoma of her right breast, axillary lymph-node dissection and immediate reconstruction with Latissimus Dorsi (LD) flap and a BIOCELL® textured silicone gel-filled implant (McGhan ST-MX410 445gr). In the following years, 2008 and 2009, she had minor scar revisions and one lipofilling session for contour aesthetic improvements. In May 2013, she presented to our outpatient clinic with an enlarged, tensed right breast without inflammation or infection signs such as redness or axillary lymphadenopathy. UE showed an anechoic and homogeneous liquid in the capsular space, surrounding the breast implant; evacuation of the seroma and replacement of the implant (BIOCELL® textured silicone gel-filled implant, McGhan ST-MX410 520gr) was planned with complete capsulectomy. Cytological analysis of the seroma showed neoplastic elements with large polymorphonucleated cells and abundant cytoplasm while histological examination of the capsule confirmed the diagnosis of a CD4+/CD30+/ALK-ALCL (Figure 2). She was admitted once more for definitive implant removal. She had a PET/CT total-body scan that did not reveal any other suspected areas. No chemotherapy was given. The patient was disease-free at last follow-up in August 2014.

Case 3

In 1999, a 56-year-old woman received bilateral breast augmentation with BIOCELL® textured silicone gel-filled implants (Inamed ST-410MF 295gr). In 2005 (BIOCELL® textured silicone gel-filled implants, Inamed ST-410MF 295gr) and 2007 (polyurethane-coated silicone implants,

Polytech Silimed 30645 290L 295ml) she underwent bilateral prosthesis replacement for capsular contracture. In July 2013, she presented to our institution, once again with bilateral capsular contracture and no other local or systemic signs. Bilateral implant replacement was done with polyurethane-coated silicone implants, Silimed 30645 290L 295ml on the right side and Polytech 30745 265 265ml on the left side. During the surgery on the right side a small amount of seroma was identified, evacuated and sent for cytological analysis together with part of the capsule. The diagnosis confirmed a CD8+/CD30+/ALK-ALCL (Figure 3). In August 2013 she was re-admitted for bilateral implant removal and complete capsulectomy. She had a PET/CT total-body scan that did not reveal any other suspected areas. No chemotherapy was given. The patient was disease-free at last follow-up in September 2014.

Case 4

In February 2006, a 41-year-old woman received quadrantectomy of the superior-lateral pole of her left breast for lobular carcinoma. In March 2006 she had wise-pattern left mastectomy, axillary lymph-node dissection, reconstruction with a BIOCELL® textured silicone gel-filled implant (Inamed 510MX-445 gr) and simultaneous contralateral breast reduction. She received 6 cycles of adjuvant chemotherapy. During the follow-up she did not show any signs of disease recurrence and in 2010 she underwent one fat-graft session of the reconstructed breast for aesthetic refinements. In August 2014 she presented an abrupt increased volume of her left breast. She preferred to do a plastic surgery visit in a private clinic and underwent UE of the left breast with evacuation of periprosthetic effusion, which was not sent for cytological analysis, and instillation of a diluted cortisone solution. The left breast swelling returned after only one month and at that time she returned to our outpatient clinic. She received an immediate bilateral breast UE that confirmed the presence of a periprosthetic effusion on the left side. It was immediately evacuated (600 cc) and sent for cytological examination showing small and big neoplastic elements that resulted CD30+, CD4+, CD15+, CD3+, CD8- and ALK- during immunohistochemistry confirming the diagnosis of BIA-ALCL (Figure 4). She had an immediate PET/CT total-body scan that did not show any other

suspected areas. She was admitted soon after for breast implant removal and complete capsulectomy. During surgery, another small (100cc) periprosthetic effusion was identified and sent for cytological analysis. Both capsule histologic examination and the second periprosthetic effusion cytological exam confirmed the primary diagnosis. No chemotherapy was given.

Retrospective analysis

We performed a retrospective analysis of all patients' histopatological records, with history of breast implant surgery that underwent secondary procedures such as breast implant replacement with partial or complete capsulectomy/capsulotomy and seroma evacuation from 2004 to 2014. Among 483 patients included in the study 458 had breast reconstruction (602 breast implants) while 25 had breast augmentation (42 breast implants). All archived histologic specimens of the identified suspected patients received a second look in order to identify any misdiagnosed cases.

Results

Of 458 patients, 226 underwent breast reconstruction with LD and prosthesis, 115 had skin/nipple-sparing mastectomy (SSM/NSM) and prosthesis and 117 had staged procedure with expander and subsequently prosthesis replacement. Breast augmentation for congenital anomalies was performed to 25 patients of which, 17 patients suffered from bilateral amastia and 8 from breast asymmetry. Fifty-eight (12%) patients underwent implant replacement for capsular contracture (Grade III-IV). Late-onset seroma (range 4 months – 2 years) occurred in 15 (3.1%) patients and in 8 of them the cytological examination was not done before surgery because of the small aliquot of the seroma formation. A combination of capsular contracture and seroma was diagnosed in 4 (0.83%) cases (Table 1). All the 77 (16%) symptomatic patients received surgical revision and eventual implant replacement and/or seroma evacuation combined with capsulectomy or capsulotomy. The histological specimens received a second look by the pathology department and although extensive samplings of the periprosthetic capsules were not done at the time no misdiagnosed cases were identified. The cytological specimens did not receive a second look because most of them were

missed. However, clinical and radiological follow-up did not show any disease until September 2014. Due to this retrospective study that revealed different treatment approaches, a multidisciplinary protocol was established for suspected BIA-ALCL patients.

Discussion

BIA-ALCL is a T-cell lymphoma and a possible direct connection with implants is supported by the reversed ratio of B-cell to T-cell lymphomas (normally 9:1) occurring to the breast in women with implants.[11-17] Moreover, all BIA-ALCL are ALK- compared to systemic ALCL where the cases can present both as ALK+ or as ALK-. Finally, prognosis differs drastically between systemic ALK- ALCL and BIA-ALCL, with the former being an aggressive disease and the latter having a more indolent course.[18-20]

Various studies proposed different etiopathogenesis hypothesis trying to associate the increased incidence of BIA-ALCL to the recent introduction of textured surface implants that lead to an excessive inflammatory reaction.[14, 21] In fact, some authors argued that this disease represented only an inflammatory response and not a real malignancy, but recent studies by Lechner et al dismissed this suggestion.[14,15]

The four new cases described in the current study add relatively new information to the growing literature. Those were presented to the National Ministry of Health and also to the FDA.

The authors performed the original operation and no patients were referred to their practice. Case 1, 2 and 4 underwent BIOCELL® textured silicone gel-filled implant placement for reconstructive purposes following mastectomy. In case 1, diagnosis of BIA-ALCL was done by excisional biopsy of the right axillary lymph node that resulted CD30+ and at the same time the contralateral side seroma was CD30+/ALK-, being the second case of bilaterally presenting ALCL currently published in literature.[22]

Case 3 received aesthetic breast augmentation with BIOCELL® textured silicone gel-filled implants. Because of the capsular contracture, the first time the patient underwent bilateral BIOCELL®

textured silicone gel-filled implant replacement while twice afterwards she received bilateral polyurethane-coated silicone implant replacement. ALCL was diagnosed 6 years after the polyurethane-coated silicone implant replacement representing the third case with CD8+, CD30+/ALK-, membrane expression profile. [16, 17, 23] .

In case 2 and 3 both patients had a negative anamnesis for common causes of late seroma or hematoma such as direct trauma, aspirin, steroids or anticoagulant use. At clinical examination case 2 showed breast swelling and case 3 capsular contracture, both without local or systemic signs of inflammation, infection or cancer symptoms and signs (fever, weight loss, night sweats, fatigue). Due to the remote consideration of ALCL diagnosis, a UE with liquid aspiration was not performed and choice treatment was implant replacement and complete capsulectomy.

The etiology of late seroma following implant placement for both reconstructive and aesthetic purposes comprises non-mechanical factors (subclinical infection due to biofilm or chemical reaction) and mechanical factors (macro and micro repetitive trauma). Mechanical causes of this phenomenon are more commonly reported than non-mechanical ones. The majority of late seromas reported in earlier reports were in patients who previously had Biocell (Allergan, Irvine, Calif.) textured implants, leading several authors to speculate that the Biocell textured surface might play a role in the pathophysiology of late seroma formation [24]. The capsule on the macropore textured implants adheres like Velcro and can be easily separated. This separation permits minor repeated trauma between the capsule and the implant excessively rough surface, creating shearing forces and therefore a seroma formation.

In 30 of 67 documented BIA-ALCL cases for which implant surface was reported in literature (including the 4 reported cases in the current study), the surface was textured in 27 (90%); the implant manufacturer was known in 23 cases of which 17 (74%) were Biocell textured implants. As previously reported, this association between textured breast implants and ALCL development suggests that the foreign biomaterial may instigate neoplastic transformation, probably by triggering a chronic inflammatory response that allows a late seroma formation [25-27].

The limitations of the retrospective study were the no extensive samplings of the periprosthetic capsules and the inability of going back and examinate the seroma fluid. As a result, no meaningful conclusion can be reached. Fortunately, all the 77 patients were disease-free at last clinical and radiological follow-up. Based on BIA-ALCL experience and on the retrospective analysis that revealed different treatment approaches, the establishment of a multidisciplinary protocol was considered mandatory in our institution for patients with breast implants and suspected signs and symptoms avoiding them unnecessary take-backs to the theater.

Some authors suggested that the physician should first rule out infection and perform a breast UE; if there is no infection evidence or infection resolution but persistent fluid collection, seroma should be aspirated and analyzed; if a palpable evidence of mass in the breast or in axilla is present, a magnetic resonance imaging (MRI) should be done, and if a diagnosis of ALCL is made from aspirated fluid (presence of ALK-1-negative T-cells and CD30 positive cells), management includes capsule and implant removal and oncologic consultation to investigate other sites of disease.[28-30]

We believe that presentation of the seroma formation is of great importance to raise suspicion for a BIA-ALCL. In our experience patients with BIA-ALCL presented with a “sterile” effusion and no cutaneous or systemic signs of inflammation and/or infection such as redness or warmth were observed (Figure 5). Nevertheless, in our protocol, all patients with late onset seroma, sudden breast swelling, capsular contracture, and/or pain are immediately enrolled to a multidisciplinary program for clinical, and ultrasound examination together with a magnetic resonance imaging of both breasts if needed. In case of seroma formation, needle aspiration is done and the liquid is sent immediately for cytological examination in order to identify neoplastic elements. A cell-block is prepared and used for the multiple histologic examinations (Papanicolaou and Giemsa coloring, immunohistochemistry staining). The liquid can be preserved at +4 °C for 2 hours if more time passes it should be mixed with an equal quantity of ethylic alcohol at 95°. In order to obtain a diagnosis of ALCL the identified tumoral cells are characterized by means of immunohistochemical

staining for the following markers: CD30, ALK, CD3, CD4, CD8. In case of a positive diagnosis, the patient is referred to the hematology department for complete clinical staging by means of a PET/CT scan and/or bone biopsy followed by breast implant removal with total capsulectomy and eventual seroma evacuation if still present.

Due to the effusion-like nature of this pathology and the presence of an extensive reactive lymphocytic infiltration that characterizes the fibrinous periprosthetic tissue the identification of tumoral cells can be challenging. For this reason, it is advisable to perform an extensive sectioning of the capsule paying attention to the areas where more fibrinous tissue is present therefore more chance for tumoral cells to be interpolated. In case of localized disease, the patient follows strict clinical and radiological follow-up every 6 months for the first two years and every 12 months until the fifth year. Follow-up should include UE of bilateral breasts, axillary and neck lymph nodes, routine blood analysis and CT total body scan. If a diagnosis of contiguous spread beyond the involved lymph node region or diffuse involvement of an extra-nodal organ is done the patient is appointed to the oncology department for further treatment according to protocol. Case 4 was the first case diagnosed through our established protocol. As a result, both the diagnosis and the patient management were done quickly and without unnecessary secondary procedures as observed for the other reported cases.

In contrast to breast carcinomas, there are very limited data on therapeutic options for lymphomas of the breast. Liu et al.[31] and Vigliotti et al.[32] recommended a sequence of full-dose (anthracyclinecontaining) chemotherapies and radiotherapy. Thompson et al.[9] performed a systematic review of the literature and mini-meta analysis of BIA-ALCL showing that chemotherapy and radiotherapy were offered to the patients either with seroma formation/mass lesions alone or seroma formation and mass lesions. Conversely, no further treatments than implant and capsulectomy were performed in some patients who presented with effusion-alone. There was a marked difference in progression-free survival between women presenting with effusion-alone compared to those presenting with a mass lesions ($p<0.001$, log rank test) and between women

having or not initial surgical implant removal ($p<0.001$, log rank test). In particular, there was no increased risk of relapse depending upon the type of therapy received (including no therapy other than surgical removal). In a more recent study, Miranda et al.[33] reviewed a literature for all published cases of BIA-ALCL from 1997 to December 2012 and contacted corresponding authors to update clinical follow-up. Most patients with BIA-ALCL who had disease confined within the fibrous capsule achieved complete remission. The authors claimed that proper management for these patients may be limited to capsulectomy and implant removal while patients who present with a mass have a more aggressive clinical course that may be fatal, justifying cytotoxic chemotherapy in addition of implants removal.

It is difficult to make therapeutic recommendations. However, based on literature reports and on our experience, it seems logical that women who present with an effusion-alone require less aggressive therapy because of the excellent outcomes in the patients who had no further therapy after surgical implant removal. We believe that chemotherapy, in particular, is not warranted in this patient subgroup and they may require nothing other than careful follow-up. The role of additional radiotherapy following implant removal is unknown and it is not recommended by a plastic surgeon consensus panel [28].

Up-to-date, only the replacement of the textured breast implant with a smooth surfaced one has been offered as a reconstructive option to patients with BIA-ALCL.[34] We believe that until definitive data emerge regarding the exact etiopathogenesis and the relationship between breast implants and ALCL the "safest" road is to offer autologous breast reconstruction if the patients desire it.

Conclusion

Despite the growing interest and numerous published studies the exact etiology of BIA-ALCL has yet to be proven. Surveillance of all patients with breast implants is needed so as to identify on time symptoms that are connected with this emerging pathology and to direct patients to specialized

centers where a multidisciplinary team can offer them the appropriate treatment. Further research and longer follow up should be done to understand the mechanism and evolution of this disease.

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Figure Legends

Figure 1. Tumor cells were found in clusters on the inner surface of the fibrous capsule surrounding the breast implant, often trapped within a fibrinoid material (left, Hematoxylin and Eosin, original magnification x200). Tumor cells were strongly positive for CD30 (center, original magnification x200) and CD4 immunophenotype (right, original magnification x200)

Figure 2. Tumor cells were found in clusters on the inner surface of the fibrous capsule surrounding the breast implant, often trapped within a fibrinoid material (left, Hematoxylin and Eosin, original magnification x200). Tumor cells were strongly positive for CD30 (center, original magnification x200) and CD4 immunophenotype (right, original magnification x200)

Figure 3. Tumor cells were found in clusters on the inner surface of the fibrous capsule surrounding the breast implant, often trapped within a fibrinoid material (left, Hematoxylin and Eosin, original magnification x200). Tumor cells were strongly positive for CD30 (center, original magnification x200) and CD8 immunophenotype (right, original magnification x200)

Figure 4. Tumor cells were found in clusters on the inner surface of the fibrous capsule surrounding the breast implant, often trapped within a fibrinoid material (left, Hematoxylin and Eosin, original magnification x200). Tumor cells were strongly positive for CD30 (center, original magnification x200) and CD4 immunophenotype (right, original magnification x200)

Figure 5. Seroma clinical presentation. (Left) BIA-ALCL seroma with no signs of inflammation and infection (right breast). (Right) Infective seroma of the left breast with evident signs of inflammation (erithema, tissue edema).

Table 1

	No of Patients	Capsular Contracture	Seroma	Capsular Contracture + Seroma	Diagnosis of ALCL	Time interval between the time of device insertion to the diagnosis of ALCL (months)
LD + Prosthesis	226	23	4	0	1	60
NSM/SSM + Prosthesis	115	16	7	1	1	101
Expander/Prosthesis	117	18	0	1	1	69
Breast Augmentation	25	1	4	2	1	77

Table 1. Suspected symptoms distribution. LD (Latissimus Dorsi); NSM (Nipple-Sparing Mastectomy; SSM (Skin-Sparing Mastectomy).

Figure 1
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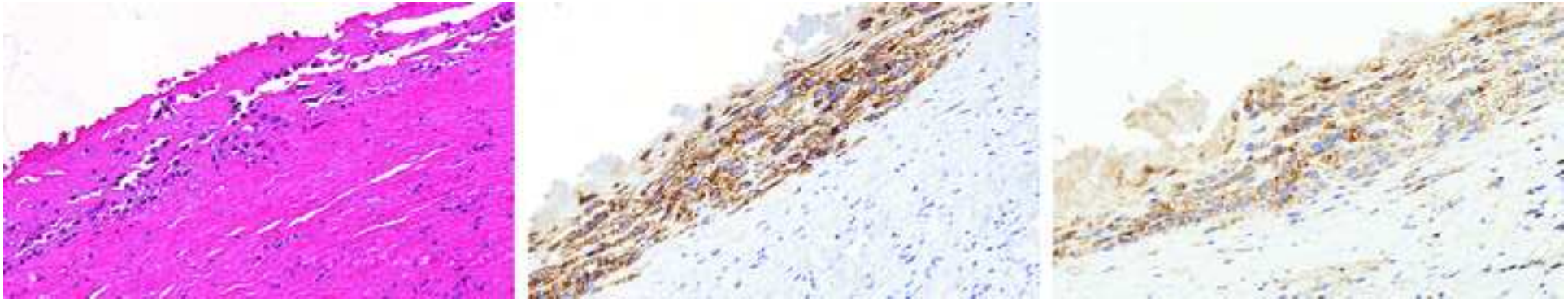

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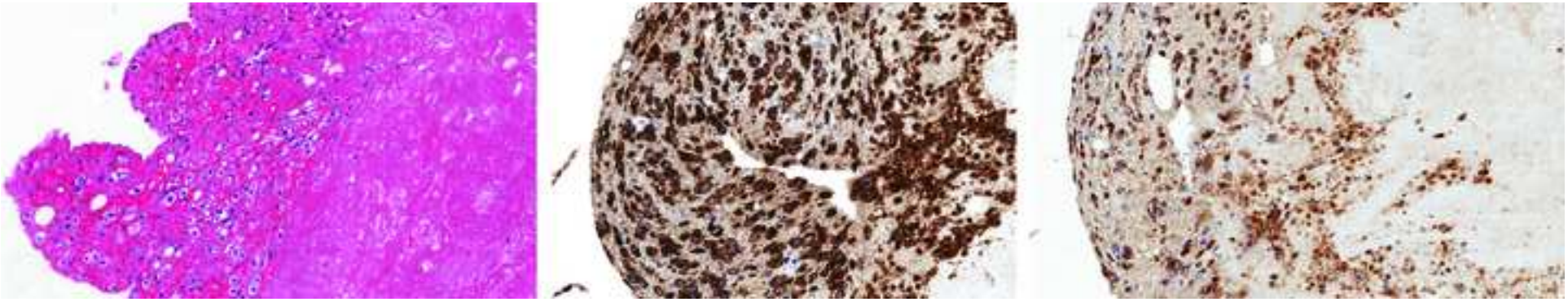

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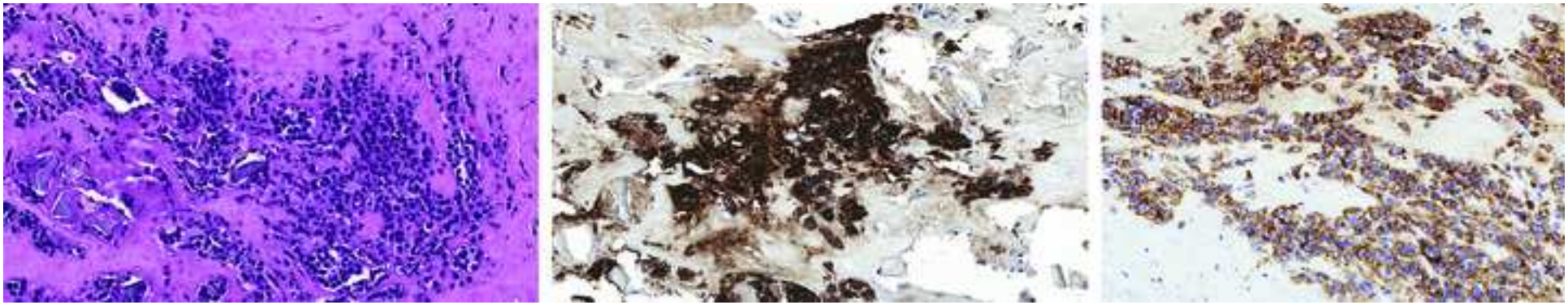

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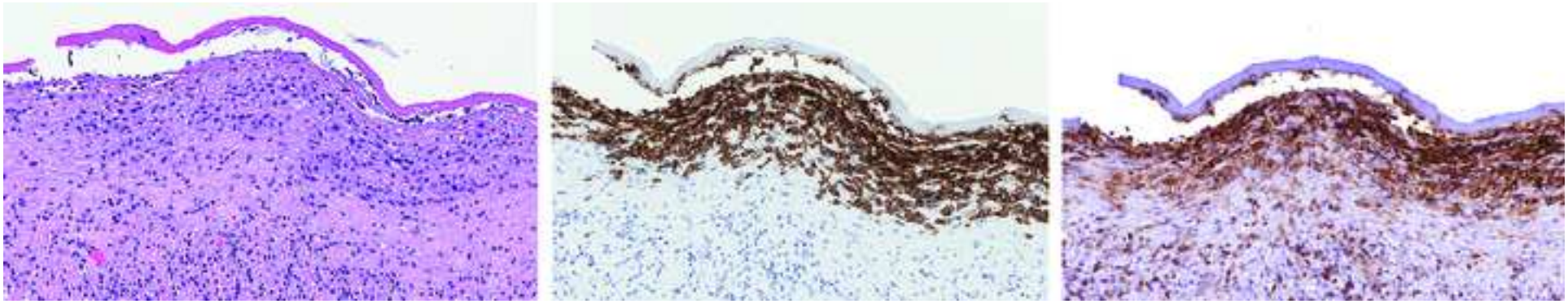

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