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BRIEF REPORT

ALK-negative anaplastic large cell lymphoma arising in the thrombus of an aortic prosthesis preceeded by clonally related lymphomatoid papulosis

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Abstract

We report on a 73-year-old male patient with recurrent thrombosis of his infrarenal aortic prosthesis. Histologically, the thrombus contained cells of an ALK-negative anaplastic large cell T cell lymphoma (ALCL). Imaging studies were negative for other lymphoma manifestations; however, 3 months before, the patient had developed skin lesions consistent with lymphomatoid papulosis type A (LypA) which were clonally related to the ALCL. Due to recurrent thrombosis of larger peripheral arteries with the presence of ALCL cells in the thrombi, the patient is now referred to systemic chemotherapy. We present the first case of ALCL manifesting in the thrombus of an aortic prosthesis. This case shows similarities to the well-established entity of breast implant-associated ALCL and anecdotal reports of ALCL occurring at the site of foreign material implants. These cells show a peculiar propensity to aggregate in vessels and thrombi, known primarily from subtypes of diffuse large B cell lymphomas associated with chronic inflammation.

Keywords Anaplastic large cell lymphoma · Lymphomatoid papulosis · PTFE · Aortic prosthesis · Breast implant-associated ALCL

Introduction

Within the last two decades, several entities of "localized lymphomas" (i.e., lymphomas presenting at a distinct anatomical site without general involvement of other body compartments) have been described and have been incorporated into the current WHO classification of tumors of hematopoietic and lymphoid tissues [1]. These entities comprise aggressive lymphomas such as primary effusion lymphoma as well as lymphomas with an indolent course such as fibrin-associated diffuse large B cell lymphoma (FA-DLBCL) and breast implant-associated anaplastic large cell lymphoma (BI-ALCL).

Here, we present the first case of an ALCL in the thrombus of an aortic prosthesis showing features similar to BI-ALCL.

Material and methods

This case was comprehensively investigated by immunohistochemistry (performed on 3-μm sections of paraffin-embedded and formalin-fixed tissue using a fully automated system (Benchmark XT System; Ventana Medical Systems Inc., Tucson, AZ, USA), in situ hybridization for EBER (Ventana), fluorescence in situ hybridization for DUSP22 translocations (IRF4/DUSP22 break apart probe, ZytoVision, Bremerhaven, Germany), clonality analysis by polymerase chain reaction [2], and next-generation sequencing (NGS) using a customized panel focusing on genes related

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to lymphomas based on the IonTorrent platform (Thermo Fisher Scientific, Carlsbad, CA, USA). For details of the NGS analysis, we refer to previous publications of our group [3, 4].

The following antibodies were used for immunohistochemistry: ALK (clone ALK01, prediluted, Ventana), CD2 (IClone MRQ-11, prediluted, Ventana), CD3 (clone 2GV6, prediluted, Ventana), CD4 (clone SP35, prediluted, Ventana), CD5 (clone SP19, prediluted, Ventana), CD7 (clone SP94, prediluted, Ventana), CD8 (clone SP57, prediluted, Ventana), CD15 (clone MMA, prediluted, Ventana), CD20 (clone L26, prediluted, Ventana), CD30 (clone BerH2+ConD6/B5, prediluted, Biocare Medical, Pacheco, CA, USA), CD79a (clone SP18, prediluted, Ventana), EMA (clone E29, prediluted, Ventana), FoxP3 (clone SP97, 1:50, Abcam, Cambridge, UK), Granzyme B (polyclonal, prediluted, Ventana), p63 (clone 4A4, prediluted, Ventana), PAX5 (clone SP34, prediluted, Ventana), Perforin (clone MRQ-23, prediluted, Ventana), pSTAT6 (clone YE361, 1:800, Abcam), and TIA1 (clone TIA-1, 1:25, Biocare).

Case presentation

A 73-year-old male patient had been treated with endovascular aortic repair (EVAR) of the infrarenal aorta due to an asymptomatic aortic aneurysm in 2012 using a Dacron® (polyethylene terephthalate [PTFE]) device. Past medical history included hypertension, polyglobulia (considered as reactive due to heavy smoking (40 pack years); there was neither genetic nor morphological evidence of a myeloproliferative neoplasm), and prostate cancer (T1c) treated by local brachytherapy in 2008 without evidence of persistent disease.

In early 2017, he presented with skin lesions consistent with lymphomatoid papulosis type A (LypA). He received topical steroids and UVB light therapy (Fig. 1f) achieving complete dermatological remission. Eight months later, he developed recurrent thrombosis of the EVAR prosthesis accompanied by embolic events of the peripheral arteries. Subsequent thrombectomy of the EVAR prosthesis showed infiltration of atypical, anaplastic CD30-positive T cells, consistent with infiltrates of an ALK-negative ALCL. The patient remained without further treatment. Seven months later, he again presented with thrombosis of the EVAR prosthesis and of peripheral arteries of the right leg. It was decided to replace the EVAR prosthesis by a conventional Y-prosthesis to control these recurrent thromboembolic events. The thrombotic specimen was histologically examined and revealed persistent focal infiltration of atypical CD30-positive T cells (Fig. 1a–c), co-expressing the T cell antigens CD2, CD3, and CD4 while being negative for ALK, CD5, CD7, CD8, EMA, FoxP3, cytotoxic T cell markers, and B cell markers (Fig. 1d). The ALCL cells did not express p63 and did not show a *DUSP22* rearrangement. T cell receptor clonality studies showed identical biclonal T cell receptor (TCR) gamma (224 bp (type V-I) and 226 bp (type V-II)) rearrangements both in the skin lesion (LypA) and in the ALCL cells in the thrombus. Next-generation sequencing of the ALCL in the thrombus revealed a hotspot activating mutation in *signal transducer and activator of transcription* (*STAT*)*6* (p.D419N, variant allelic frequency (VAF) 33.5%) and a truncating mutation in *Lysine Methyltransferase 2D* (*KMT2D*) (p.V3122fs, VAF 23.7%). Consistent with the presence of the *STAT6* activating mutation, the tumor cells of the ALCL showed nuclear phospho-STAT6 expression by immunohistochemistry (Fig. 1e).

The confirmation of recurring ALK-negative ALCL infiltrates in the thrombus of the aortic graft led to the formal staging of the patient. A bone marrow trephine biopsy and PET-CT were performed, which did not reveal other sites of lymphoma involvement. However, 4 months later, the patient developed ischemia of his left leg due to thrombosis of the left iliac artery. Histological examination showed infiltrates of the previously diagnosed ALCL. Thus, it was decided to treat the patient with systemic CHOP-based chemotherapy.

Discussion

Here, we described a case fulfilling all morphological and immunophenotypical characteristics of ALK-negative ALCL including a clonal TCR-rearrangement and *STAT6* and *KMT2D* mutations. The presence of the hotspot activating *STAT6* mutations could be corroborated by phosphorylated (active) STAT6-protein expression in the tumor cells.

Interestingly, this lymphoma arose in or at least had preferentially spread to foreign material (EVAR made of PTFE) and fibrin. Furthermore, the same clonal cells have also been detected in a skin lesion formally fulfilling diagnostic criteria of LypA.

Up till now, more than 300 cases of BI-ALCL have been described in the literature [5], most of them showing an indolent course and the majority being "cured" by the removal of the implant. Cases of "localized" ALCL have also been anecdotally described in a metal implant of the tibia without evidence of systemic involvement [6], in the vicinity of a silicon band bariatric implant of the stomach [7], next to a silicon gluteal implant [8], and in the subcutaneous tissue of a patient with dystrophic calcifications due to long-standing dermatomyositis [9]. However, so far—to the best of our knowledge—no case of ALCL in thrombotic material has been described.

The pathogenesis of BI-ALCL has not been fully elucidated yet. Several studies have suggested that their occurrence is linked to the texture of the implants, which might promote the development of a biofilm of bacteria in a chronically

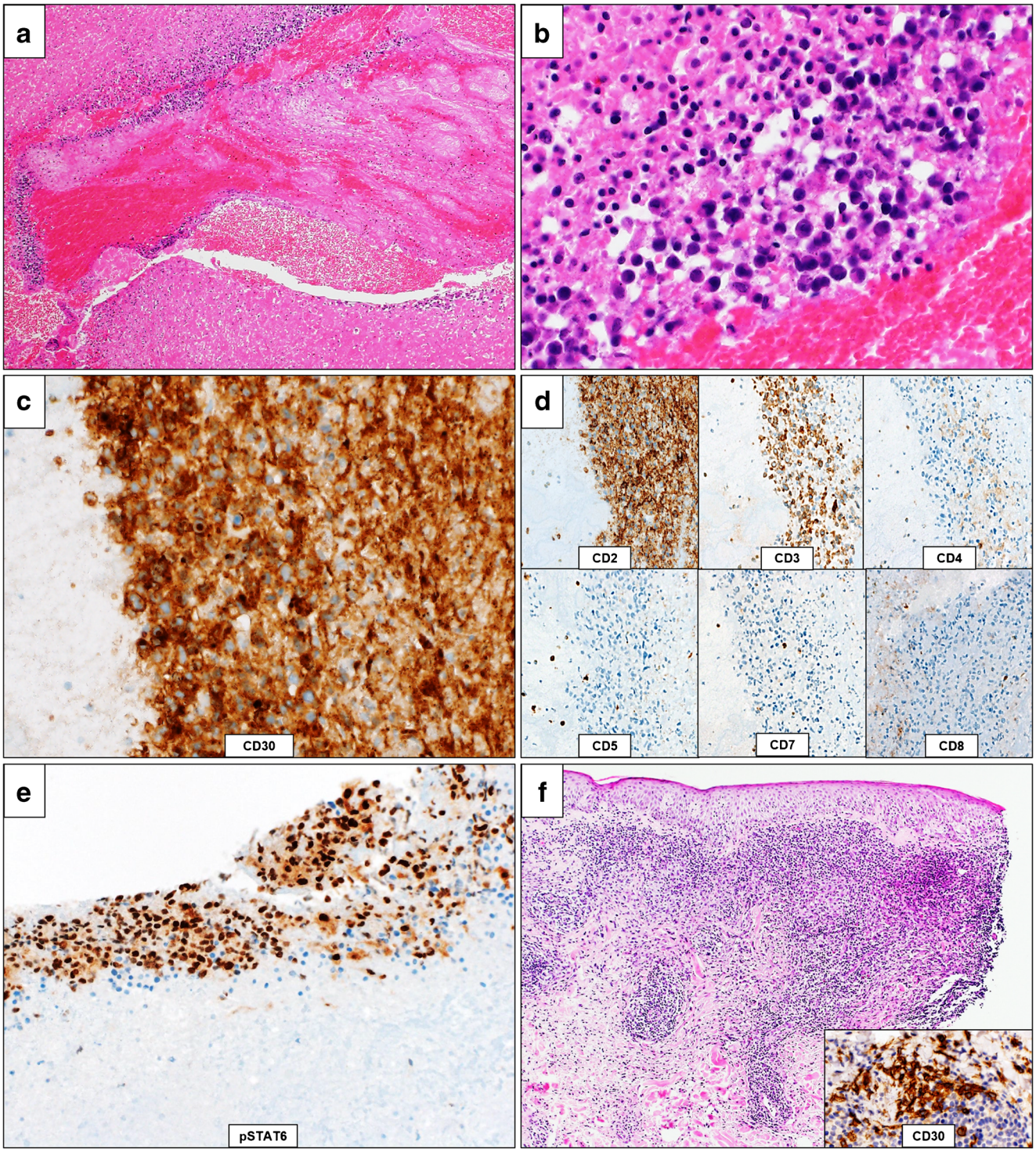

Fig. 1 **a** Overview showing the thrombus with large atypical cells at its surface (HE, × 50). **b** Higher magnification of the large atypical cells showing classical features of anaplastic large cell lymphoma with hallmark cells (HE, × 200). **c** Expression of CD30 in the lymphoma cells (× 100). **d** Expression of T cell markers: the tumor cells expressed CD2, CD3, and CD4 (weakly and focally), while being negative for CD5, CD7, and CD8. In all cases, internal positive controls of reactive T cells were present (immunohistochemical stains, × 100). **e** Expression pSTAT6 (× 100). **f** Skin lesions showing lymphoid perivascular dermal infiltrates containing large atypical cells (HE, × 50), which were positive for CD30 (insert, × 100)

proinflammatory environment [10, 11]. Furthermore, a direct proinflammatory effect of silicone cannot be excluded [12]. In the case of ALCL associated with the metal implant, the authors also speculated that a chronic antigenic stimulus—potentially derived from a reaction to metal particles, which might have induced the release of proinflammatory substances

by macrophages—was responsible for the occurrence of the ALCL at this site [6]. The PTFE device used in our patient also has a rough surface known to induce a normally mild inflammatory response with formation of granulation tissue, which ensures stability of the surrounding tissue and prevents dislocation of the graft [13]. In BI-ALCL, tumor cells have been described as either freely floating in the seroma fluid or attached to fibrin, and some cases also show infiltration of the implant capsule or the surrounding tissue [14]. The single cases of localized ALCL in other locations also document the presence of ALCL cells in close contact to fibrin [6–8]. In our case, ALCL cells were restricted to the fibrin deposits of the partially thrombosed graft, and there was no evidence of ALCL cells in the surrounding fibrous tissue. Having these findings in mind, we hypothesize that the fibrin and the thrombotic material itself might also be important for the tumor cells as they provide their primary surroundings.

Similarly, several cases of DLBCL arising in fibrin clots (FA-DLBCL) have been described, with most of them developing in the area of heart valves and few cases also occurring in the aorta [15]. All cases investigated for the presence of Epstein-Barr virus (EBV) were positive. Recurring thrombosis—also after resection of the initial lesion—is described in the literature as being a potentially fatal complication of this disease. Its pathogenesis remains obscure, but both the presence of foreign material and chronic inflammation are thought to have a contributory effect; furthermore, local immunosuppression leading to EBV reactivation is another potential contributing factor [15].

Our patient also developed cutaneous lesions with CD30-positive atypical cells prior to the removal of the first thrombus; they were treated by local therapy and have been in complete remission since. These lesions were diagnosed as LypA based on an integrative clinicpathological appraisal. It is well known that lymphomatoid papulosis in general can be considered an indicator lesion of lymphomas including ALCL, yet it is not necessarily related to the systemic lymphoma [16]. Interestingly, we demonstrated identical clonal restriction and phospho-STAT6 expression of the atypical CD30 positive T cells in the skin biopsies as in the lymphoma cells of the thrombus. Retrospectively, and bearing in mind the molecular results, the skin lesions did not qualify for the diagnosis of ALCL infiltrates. One series on BI-ALCL described the presence of lymphomatoid papulosis in one case, yet it did not report whether the two lesions were clonally related or the time sequence of them [17]. Taken together, it could be speculated that the circulating LyPA cells have found an immunoprivileged niche in the thrombotic material which fostered the development of an overt ALCL. ALCL is the second most common lymphoma-subtype occurring in the setting of LyP [18]. Interestingly, there has been no recurrence of the LyPA since initial local therapy in early 2017.

The genetic landscape of ALCL has been investigated in several larger cohorts, and ALCL has been shown to harbor frequent *JAK1* and *STAT3* mutations [19], which are also found in some BI-ALCL cases [14]. The *STAT6* mutation discovered in our case—and corroborated by phospho-STAT6-protein expression—is a hotspot activating mutation previously described in follicular lymphoma and Hodgkin lymphomas. Importantly, STAT6 activation, which is important for interleukin 4–mediated signaling, can be found in both B cell and T cell lymphomas [20]. Another feature being uncommon in BI-ALCL and other localized ALCLs (described in the cases related to the gluteal implant, the gastric bariatric band and the dystrophic calcifications) is the absence of expression of cytotoxic markers in our case. This also shows the heterogeneity of this entity.

To conclude, here, we present the first case of ALCL in a thrombus of an aortic prosthesis. This case increases the spectrum of "localized lymphomas" and should foster the search for other cases of localized ALCL beyond the setting of breast implants. We furthermore showed a prototypic activating *STAT6* mutation confirmed by protein expression, which has been described in other lymphomas but not in ALCL. As in the case of other foreign body or implant-associated lymphomas, further research is warranted to decipher the pathogenesis of this peculiar subtype of lymphomas to answer the question whether it is the non-human material, the chronic inflammation, or the factors inherent in the thrombus itself that lead to lymphoma development in this subset of patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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