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Published on: 10 Apr 2018 - Virchows Archiv (Springer Berlin Heidelberg)

Topics: Anaplastic large-cell lymphoma, Large cell, Breast implant and Lymphoma

Title: Dual JAK1 and STAT3 mutations in a breast implant-associated anaplastic large cell lymphoma.

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Journal: Virchows Archiv : an international journal of pathology

Year: 2018 Oct

Issue: 473

Volume: 4

Pages: 505-511

DOI: 10.1007/s00428-018-2352-y

Virchows Archiv

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--Manuscript Draft--

Manuscript Number:	VIAR-D-18-00062R1
Full Title:	Dual JAK1 and STAT3 mutations in a breast implant-associated anaplastic large-cell lymphoma.
Article Type:	Brief Report
Corresponding Author:	Laurence De Leval Centre Hospitalier Universitaire Vaudois Institut Universitaire de Pathologie Lausanne, SWITZERLAND
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Centre Hospitalier Universitaire Vaudois Institut Universitaire de Pathologie
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	Laurence de Leval
Order of Authors Secondary Information:	
Funding Information:	
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Response to Reviewers:	A separate file with responses to reviewers will be submitted.

Dual *JAK1* and *STAT3* mutations in a breast implant-associated anaplastic large-cell lymphoma.

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Abstract

Breast implant-associated anaplastic large-cell lymphoma (BI-ALCL) is rare and knowledge on its underlying genetics is limited. A few somatic mutations have been reported in four seroma-associated cases. Here, we characterized paired BI-ALCL samples from a patient whose disease presented as a solid tumour and recurred as an *in situ* capsular lesion. We identified two pathogenic gain-of-function hotspot mutations in the kinase domain of *JAK1* (G1097V) and in the SH2 domain of *STAT3* (S614R) in both specimens, demonstrated nuclear p-STAT3 in the lymphoma cells and found no rearrangements of *DUSP22, TP63* or *VAV1*. Our findings reinforce the notion that mutation-induced activation of the JAK/STAT pathway represents a recurrent oncogenic mechanism in both clinical presentations of BI-ALCL; moreover the co-occurrence of dual *JAK1/STAT3* mutations as observed in our case suggests pathogenic mechanisms overlapping with those of systemic ALK-negative ALCL.

Introduction

Breast implant-associated anaplastic large-cell lymphoma (BI-ALCL) recently described as a distinctive form of CD30+ anaplastic large-cell lymphoproliferation, was introduced as a new provisional T-cell lymphoma entity in the 2017 WHO classification of haematological malignancies [1]. While the morphological and immunophenotypical features of BI-ALCL are indistinguishable from those of other ALK-negative ALCL, the specificity of BI-ALCL is its clinical presentation adjacent to a breast implant. Most cases confined to the periprosthetic effusion and capsule (seroma or « *in situ* » lymphoma) have excellent outcomes, and a minority of patients present with a breast tumour mass, which is an adverse prognostic factor [2,3].

Yet, information on the genetic alterations associated to BI-ALCL is essentially limited to data derived from a few lymphoma specimens, all with seroma-associated presentation (summarized in **Table 1**). [4] [5] [6] [7] Here we report genetic findings in paired BI-ALCL samples of a patient whose disease presented as a solid tumour and recurred as an *in situ* capsular lesion.

Methods

Both specimens were routinely processed after formalin fixation and paraffin embedding in the Department of Pathology of the Institute Jules Bordet (Brussels, Belgium). Immunophenotyping was performed with routinely used antibodies on Ventana Benchmark/Ultra instruments. Immunohistochemistry for phospho-STAT3 (Tyr205) was performed with the D3A4 rabbit monoclonal antibody (Cell Signaling Technology, Danvers, MA, USA ; ref. 9145) diluted at 1/100

and incubated overnight at 4°C after 3 minutes antigen retrieval in EDTA pH 9 in a pressure cooker.

Fluorescent in situ hybridization

Laboratory-developed FISH probes (Institute of Pathology, Lausanne) using bacterial artificial chromosome (BAC) combinations were used to explore rearrangements of *DUSP22/IRF4, TP63* and *VAV1.* For *DUSP22/IRF4*, break-apart probe consisted of telomeric RP3-416J7, labeled with Spectrum Orange; and centromeric RP11-615C17 and CTD-3139L20 labeled with Spectrum Green. For *TP63*, break-apart probe consisted of telomeric RP11-24F1, labeled with Spectrum Orange; and centromeric RP11-53D15 labeled with Spectrum Green. For *VAV1*, break-apart probe consisted of telomeric RP11-828J24, RP11-809P6 and RP11-134L9 labeled with Spectrum Green; and RP11-876D1, CTD-3131P and RP11-1137G4 labeled with Spectrum Orange.

Targeted sequencing

DNA extracted from primary and recurrent FFPE tumour samples after enrichment by scraping under microscopic control, was used to prepare DNA libraries with the KAPA HyperPlus library preparation kit (Roche). Target enrichment of the DNA libraries was performed by hybridization capture using a custom design of xGen® Lockdown® Probes (Integrated DNA Technologies) covering the full coding sequences of 26 genes recurrently mutated in various mature T-cell neoplasms (*ARID1A, ATM, BCOR, CARD11, CCR4, CD28, CTNNB1, DDX3X, DNMT3A, FYN, IDH2, IRF4, JAK1, JAK3, KMT2D, PIK3CD, PLCG1, PRKCB, RHOA, SETD2, STAT3, STAT5B, TET2, TNFRSF1B, TP53, VAV1*). Enriched libraries were sequenced on a MiSeq instrument (Illumina). Raw reads were aligned to the hg19 human genome assembly using BWA aligner and further processed following GATK best practices (https://software.broadinstitute.org/gatk/best-

practices/). The list of variants was obtained combining calls from both VarScan (2.4.2) and MuTect2 variant callers packages using default settings. Variants were further filtered based on local coverage (>50), number of altered reads (>5), allele frequency (>1%) and strand bias.

Case report

The woman born in 1943 had elective bilateral insertion of silicone-filled breast implants (McGhan) in 1992 for cosmetic reasons. She presented in May 2011 with a right breast mass; MRI imaging showed a 3.9 cm solid lesion, no periprosthetic effusion, and enlarged right axillary lymph nodes. A PET CT-scan demonstrated a voluminous hypermetabolic lesion (SUV 13.3) in the lower right breast adjacent to the prosthesis and multiple slightly hypermetabolic lymph nodes in the right axilla (**Figure 1**). A tumorectomy was performed which comprised a 2.8 cm solid and partially necrotic infiltrating tumour made up of cohesive sheets of large anaplastic lymphoid cells (**Figure 2A-B**), abutting to the resection margin. By immunohistochemistry the tumour cells were strongly positive for CD30, positive for CD8 and CD45 RO, negative for ALK, EMA, CD2, CD3, CD4, CD5, CD7, CD15, CD20, CD45, CD56, and had an activated cytotoxic phenotype (granzyme-B+, perforin+) (**Figure 2 C-E**). A staging bone marrow biopsy was negative. The patient was treated with 5 cycles of CHOP (cyclophosphamide, daunorubicin, oncovin, prednisone) resulting in complete metabolic response. Consolidation with 2 cycles of high-dose methotrexate 3 g/m² was subsequently administered, followed by autologous stem cell transplantation after BEAM conditioning in November 2011. In 2012 both prostheses were replaced by silicone-filled implants with biocell-textured shell (Allergan). In 2015 MRI demonstrated a rupture of the right prosthesis, and both prostheses were removed. The right

periprosthetic capsule was macroscopically irregular and gritty and on histology showed a proliferation of large anaplastic cells confined to the surface and admixed with fibrin (**Figure 2F-G**). The immunophenotype was similar to that of the 2011 lesion, except for loss of CD8 expression and detectable EMA expression. An identical monoclonal rearrangement of *TRG* and *TRB* genes was demonstrated in both specimens. The patient did not receive further treatment and was last seen in July 2017, with no evidence of recurring disease.

The patient consented to further genetic analyses. FISH studies with break-apart probes for *DUSP22/IRF4*, *TP63* and *VAV1* loci showed no evidence of rearrangement (**Figure 2H-I**). We performed targeted deep sequencing analysis of both primary and recurrent tumors, using a panel of 26 genes relevant to T-cell lymphoma oncogenesis. Two pathogenic hotspot mutations, one in the kinase domain of *JAK1* (c.3290G>T (p.G1097V)) and the other in the SH2 domain of *STAT3* (c.1840A>C (p.S614R)), were detected in both specimens. Moreover, an additional *JAK1* truncating mutation (c.549dupT (p.D184*)) was detected in the first tumour only. Reflecting the presumed mutation-induced STAT3 activation, immunohistochemistry showed high levels of nuclear pSTAT3 expression in most tumour cells (**Figure 2J**).

Discussion

We report a patient with breast implants who developed BI-ALCL in the form of an unusual tumor mass presentation, was set to remission after surgical resection and systemic and intensive systemic treatment, and recurred four years later with a seroma-associated *in situ* capsular lesion in the same breast. The clinical management of the patient in 2011 was not in line with the current recommendations that would require upfront removal of the prosthetic

implants, and indeed the delay for prosthesis resection could have been responsible for the tumor recurrence, since one can suspect that the capsular involvement might have been present since the very beginning, although at an infra-clinical state with no evidence of effusion. Both clonality studies and targeted deep sequencing results, provided compelling evidence that the solid and seroma-associated lesions represented an identical clone, qualifying the second lesion as tumour recurrence. The tumor at presentation likely represents clonal evolution from a precursor lacking the second *JAK1* mutation, and the recurrence evolved from the latter.

Very limited information is available in the literature regarding the genetic lesions underlying BI-ALCL (**Table 1**). [4] [5] [6] [7] In total, karyotypes from three cell lines derived from BI-ALCLs and mutational analysis of seven primary tumor samples have been reported. The BI-ALCL-derived cell lines had markedly abnormal complex karyotypes with a near-diploid or a hypertriploid pattern)[4,5]. In contrast, of the seven cases of BI-ALCL that were successfully analyzed by whole exome or targeted next-generation sequencing using a large panel of 465 cancer-associated genes, only four showed a small number of somatic variants, and three of the five cases successfully analyzed with a large cancer-oriented sequencing panel were wild-type for all tested genes [6] [7]. Strikingly, two of the four cases harbored a STAT3 S614R variant (as the sole abnormality in one case and in combination with pathogenic *TP53* and *SOCS1* mutations in the other), and another case harbored *JAK1* (G1097V) somatic variant, indicating recurrent JAK/STAT mutations in BI-ALCL. The S614R variant of *STAT3* is known as a gain-of function variant and has a been found in a variety of T-cell neoplasms including T-LGL leukemia, extranodal NK/T-cell lymphoma, and systemic ALK-negative ALCL [8]. The *JAK1* G1097V variant is also likely activating, since *JAK1* mutants at the 1097 position reported in other ALK-negative

ALCLs have activating function [9]. Accordingly, functional studies on the BI-ALCL cell lines showed evidence of STAT3 activation, and the pharmacological inhibition of STAT3 induced *in vitro* cell death [5].

Our case was characterized by coexistent *JAK1* G1097V and *STAT3* S614R mutations. While mutation-induced activation of the JAK/STAT pathway constitutes a recurrent oncogenic mechanism in a variety of T-cell malignancies [10-14], the co-occurrence of dual *JAK1/STAT3* mutations as observed in this BI-ALCL case represents a peculiar mutational pattern that yet has been reported only in a subset of nodal ALK-negative ALCLs [9], suggesting that the pathogenic mechanisms operating in BI-ALCL overlap with those of systemic ALK-negative ALCLs. The significance of the additional *JAK1* truncating mutation found in the first tumour only is uncertain: similar mutations in gynecological tumours might interfere with IFNγ-mediated mechanisms of immune surveillance[15], but their impact in haematological neoplasias is unknown. Moreover, the same mutational pattern in the paired samples in this case indicates that the two types of clinical presentations of BI-ALCL (as a tumour or in association to a seroma) may not reflect molecularly distinct subtypes. Interestingly, including this case, the *JAK1* G1097V and *STAT3* S614R mutations were found in two and three BI-ALCL cases, respectively (**Table 1**). Since numerous other hotspot mutations in these genes are found in other haemopathies [8], despite the small number of BI-ALCL cases yet analyzed, it might be suggested that *JAK1* G1097V and *STAT3* S614R variants found by us and others could represent preferential recurrent drivers in this disease.

Table 1

Summary of published genetic and molecular features of BI-ALCL specimens

Reference	Clinical features	Specimen	Analysis	Results	Comments
Patient 1 - Lechner MG et al. Cancer 2011	F/42 yrs-old; right recurring effusion, 3.5 years after cosmetic insertion of implants; treated with surgery (bilateral implant removal +capsulectomy) and radiation therapy; in remission @ 6 years	T-cell breast lymphoma (TLBR)-1 cell line established from culture of the original tumor on a stromal feeder layer in the presence of IL-2	Conventional cytogenetics	Complex karyotype: partial trisomy 2, addition involving 5p, deletion of 10p, unbalanced translocation between chromosomes 12 and 17, and monosomy 16 and 20; presence of subclonal populations with the addition of unknown genetic material to the short arm of chromosomes 13, 15 and 15	All three TLBR cell lines showed: increased levels of cleaved, activated NOTCH1; and activation of STAT3 signaling (nuclear expression of pSTAT3) and sensitivity to pharmacological STAT3 inhibition in vitro.
Blombery P et al. Haematologica 2016	Id.	Effusion cytology fluid (and uninvolved bone marrow as germline control)	Whole exome sequencing (mean target coverage 113x for tumor DNA)	Somatic mutation ***STAT3* S614R** (c1840A>C) Copy number changes: 1p and 10p copy number losses, 19p copy number gain	Pathogenic gain-of-function mutation inducing STAT3 activation
Patient 2 - Lechner MG et al. Clin Cancer Res	F/43 yrs-old; unilateral recurring effusion, after cosmetic insertion of implants; treated with surgery	TLBR-2 cell line established from culture of the	Conventional cytogenetics	Hypertriploid complex karyotype with a modal number of chromosomes of 76, gains of chromosomes 1, 2, 5, 6, 10, 11, 14, 17,	

2012	(bilateral implant removal + capsulectomy); early local recurrence and distant dissemination of disease, resistant to chemotherapy; dead of disease @ 9 months	original tumor in the presence of IL-2		and clonal loss of one copy of chromosome 18, relative to a triploid genome.	
Patient 3 - Lechner MG et al. Clin Cancer Res 2012	F/45 yrs-old; unilateral recurring effusion, after cosmetic insertion of implants; treated with surgery (bilateral implant removal + capsulectomy) and radiation therapy; in remission @ 14 months	TLBR-3 cell line established from culture of the original tumor in the presence of IL-2	Conventional cytogenetics	Hypertriploid complex karyotype with a modal number of chromosomes of 81, gains of chromosomes X, 2, 5, 7, 8, 10, 11, 12, 14, 19, 20, 21 and 22, and loss of one copy of chromosomes 9, 16 and 17, relative to a triploid genome.	
Patient 4 - Blombery P et al. Haematologica 2016	F/56 ys-old; left effusion 7 years after cosmetic insertion of implants; treated with surgery (implant removal + capsulectomy); in remission @6 months	Effusion cytology fluid (and germline control)	Whole exome sequencing (mean target coverage 145x for tumor DNA)	Somatic mutation ***JAK1* G1097V** (c.3290_3291delinsTT) No copy number changes	Probably pathogenic mutation affecting a codon frequently mutated in ALK-negative systemic ALCL, and other variants resulting from amino acid changes at this site result in constitutive JAK1 activation.
Patient 5-	F/54 yrs-old; right effusion 5 years	Microdissected	Targeted deep	Somatic mutation	Inactivating nonsense mutation

Di Napoli A et al. British J Haematol	after reconstructive insertion of implant (invasive ductal breast carcinoma)	tumor cells of FFPE BI-ALCL samples and matched germline DNA	sequencing using a panel of 465 cancer-associated genes (average read depth 400x)	***DNMT3A* W176X** (c.528G>A) (VAF 39%) Copy number changes not analyzed	of *DNMT3*.
Patient 6- Di Napoli A et al. British J Haematol	F/47 yrs-old; left effusion and contralateral axillary lymph node after reconstructive insertion of implant (breast cancer)	Microdissected tumor cells of FFPE BI-ALCL samples and matched germline DNA	Targeted deep sequencing using a panel of 465 cancer-associated genes (average read depth 400x)	Somatic mutations ***SOCS1* P83fs** (c.248_293del) (VAF 10%) ***STAT3* S614R** (c.1840A>C) (VAF 32%) ***TP53* D259Y** (c.775G>T) (VAF 37%) Copy number changes not analyzed	Coexisting gain-of-function mutation of *STAT3* and deleterious loss-of-function of *SOCS1* (negative feed-back regulator of the JAK/STAT pathway) likely converging to activate the JAK/STAT pathway
Patient 7 - Letourneau A et al. current report	F/68 yrs-old; right breast mass and homolateral enlarged axillary lymph node, without effusion, 9 years after cosmetic insertion of implants; treated with surgery (tumorectomy without implant removal), and high-dose chemotherapy + autologous stem cell transplantation; followed by removal of implants and	Microdissected tumor of FFPE breast tumorectomy	Targeted deep sequencing using a panel of 26 genes relevant to T-cell lymphomagenesis (mean read coverage 946X)	Mutations ***JAK1* D184X** (c.549dupT) (VAF 16%) ***JAK1* G1097V** (c.3290G>T) (VAF 45%) ***STAT3* S614R** (c.1840A>C) (VAF 26%) FISH analyses: no rearrangement of *DUSP22/IRF4*, *TP63* and *VAV1* loci	

	reinsertion of new prostheses				
Letourneau A. et al. current report	Rupture of the right implant 3 years later; treated with surgery (implant removal + capuslectomy); in remission @6 years after initial diagnosis	Microdissected tumor of FFPE implant capsulectomy	Targeted deep sequencing using a panel of 26 genes relevant to T-cell lymphomagenesis (mean read coverage 1517X)	Mutations ***JAK1* G1097V** (c.3290G>T) (VAF 72%) ***STAT3* S614R** (c.1840A>C) (VAF 26%)	Same *TCR* rearrangement as in the tumor specimen. Disappearance of the *JAK1* D184X variant and increase VAF of the *JAK1*G1097V variant suggest loss of the allele harboring the deleterious mutation.

VAF: variant allele frequency

Legend to Figures

Figure 1

PET-CT scan at diagnosis showing a hypermetabolic mass adjacent to the right breast implant on a frontal section.

Figure 2

(A-B) BI-ALCL at presentation consisting of an infiltrative and partially necrotic (*) tumor mass composed of cohesive large anaplastic cells (haematoxylin and eosin); (C-E) immunohistochemical stainings of the tumor cells showing strong positivity for CD30 (C) and granzyme B (D), and weak positivity for CD8 (E) (immunoperoxidase); (F-G) recurrent "*in situ*" BI-ALCL consisting of an anaplastic cell proliferation associated to fibrin at the surface of the pseudocapsule (haematoxylin and eosin); (H-I) FISH analyses using break-apart probes for the *DUSP22/IRF4* locus (H) and *TP63* locus (I) showing colocalized signals only, indicative of the absence of rearrangements; (J) immunohistochemical staining showing nuclear expression of pSTAT3 (Tyr705) (immunoperoxidase).

Notes

AL and DM performed research; MM and RD contributed essential clinical information; BB and EM analysed the data and wrote the paper; LDL designed research and wrote the paper.

Compliance with ethical standards.

No funding.

The authors declare no conflict of interest.

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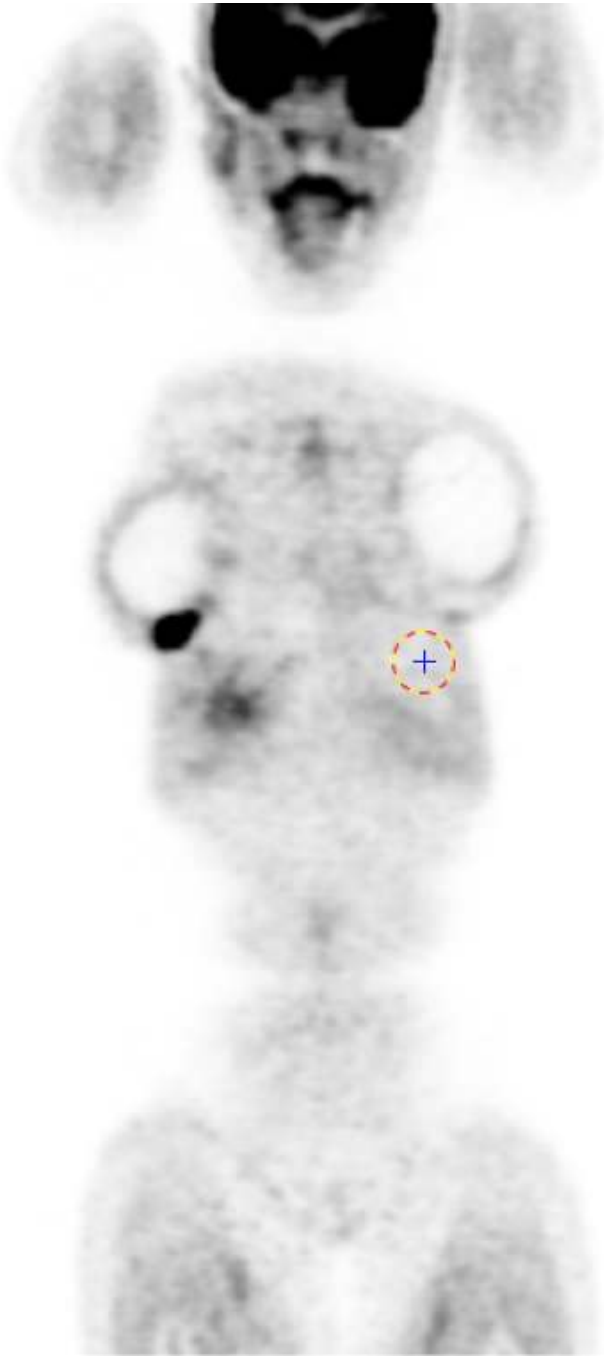
Figure



Figure