J Hematopathol (2013) 6:237–244
DOI 10.1007/s12308-013-0184-x

CASE REPORT

T-lymphoblastic proliferation and florid multifocal follicular dendritic cell proliferation occurring in hyaline-vascular Castleman disease in a patient with a possible familial predisposition

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Received: 16 January 2013 / Accepted: 12 April 2013 / Published online: 3 May 2013

Abstract Hyaline-vascular Castleman disease (HVCD) often presents as unicentric disease which is usually cured by surgical resection. Here, we report a case of a 23-year-old man with HVCD in the mediastinum, in which an apparently indolent T-lymphoblastic proliferation and extensive organoid proliferation of follicular dendritic cells were also present. The patient had no systemic involvement and no further disease at follow-up. In addition, there is a possible unique family history of HVCD. This case highlights an interesting combination of elements, mostly likely benign in nature.

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Keywords T-lymphoblastic proliferation · TdT · Castleman disease · Follicular dendritic cell tumour

Introduction

Castleman disease (angiofollicular lymph node hyperplasia) encompasses a group of entities defined by lymphadenopathy with aberrant follicles and interfollicular vascular hyperplasia, without monoclonal lymphoid proliferation. The presentation and disease course are variable, and several subtypes are recognised based on various clinicopathological features including morphology (hyaline-vascular vs plasma cell rich), extent of disease (unicentric vs multicentric) and patient immune status [1, 2].

The hyaline-vascular variant of Castleman disease (HVCD) usually presents as unicentric disease, often involving a thoracic node in immunocompetent young adults without systemic symptoms. Its pathogenesis is not well understood, although underlying follicular dendritic cell (FDC) abnormalities have been described including overexpression of epidermal growth factor receptor (EGFR) [3], HMGIC gene rearrangement [4], clonal proliferation of stromal elements [5] and developmental block of FDC precursors [6]. HVCD is usually cured by complete surgical excision [7] although it may be complicated by follicular dendritic cell neoplasms [8], angiomyoid proliferation [9] and vascular neoplasia [10]. In one report [8], sequential biopsies in a patient with HVCD demonstrated progressive FDC proliferation from an initially orderly expansion, to focally infiltrative growth and ultimately to an overgrowth consistent with FDC sarcoma.

The plasma cell variant of CD (PCCD) is typically (but not invariably) multicentric, is associated with dysregulation

of IL-6 and frequently presents with constitutional symptoms. HHV-8 infection has been implicated in immunosuppressed or HIV-positive patients, whilst an unknown infectious agent is postulated in the aetiology of other cases [11]. PCCD may be associated with monotypic plasma cell proliferations and POEMS syndrome, whilst HHV-8-associated CD may progress to lymphoma and Kaposi sarcoma.

Indolent T-lymphoblastic proliferation (ITLBP) is a concept introduced by a small number of case reports describing a localised proliferation of T lymphoblasts outside the bone marrow and thymus without systemic dissemination. This has been described in the nasopharynx [12], in oropharynx and adjacent cervical lymph nodes [13] and in two cases the ITLBP occurred within an intrahepatic hepatocellular carcinoma [14, 15]. ITLBL has been described in association with CD, initially in a case report of HVCD occurring in a 71-year-old man [16] who had a history of rheumatoid arthritis treated with methotrexate and prednisolone and recently in a study by Ohgami et al. [17] describing T-lymphoblastic populations in a majority of CD cases, although only a minority showed dense collections. A recent report [18] described an aggressive FDC sarcoma of mesenteric origin harbouring an immature T-lymphoblastic proliferation. The patient died from complications associated with metastatic FDC sarcoma within 2 years, without evidence of disseminated T-lymphoblastic lymphoma. The study by Ohgami [17] noted T-lymphoblastic proliferations in three cases of CD with concurrent follicular dendritic cell tumours and in one case of an isolated follicular dendritic cell tumour.

Here, we document a case of HVCD, presenting in the mediastinum of a young man, within which both a multifocal T-lymphoblastic proliferation and a florid multifocal FDC proliferation occurred. This case adds another example to the literature of probable ITLBP occurring outside the thymus in association with HVCD, also associated with a florid multifocal FDC proliferation which may have the potential to progress to FDC sarcoma. Further, there is a unique family history in that the patient's mother and one of her two sisters had also been diagnosed previously with HVCD.

Case history

A 23-year-old male, investigated for upper respiratory tract symptoms, was incidentally found to have a mediastinal mass. Further CT of the neck, chest and abdomen did not detect lymphadenopathy, although bony sclerosis of uncertain significance involving the vertebrae and pelvis was noted. He had rheumatic fever as a child and was on long-term prophylaxis with penicillin. He was otherwise well with normal full blood count, electrolytes and LDH levels. There were no paraproteins or serum-free light chains. Follow-up bone marrow biopsy result was normal. At surgical resection, the mediastinal mass was located in the aorto-pulmonary window and was clearly unrelated to the thymus.

His family history includes histologically confirmed HVCD in his mother (aged 44 years, retroperitoneal mass) and one of her sisters (age at biopsy, unknown; location, within the chest). In these family members, there has been no documented relapse after long follow-up periods. The pathology was reported in Bangladesh over 10 years ago, and the specimens cannot be reviewed.

At last follow-up, 30 months after presentation, the patient remains well without evidence of disease. In particular, there is no evidence of disseminated lymphoblastic lymphoma or leukaemia nor of metastatic FDC sarcoma.

Materials and methods

From the resected 'mediastinal lymph node', samples were taken for flow cytometry and cytogenetics. Representative sections (six blocks) were fixed in 10 % neutral-buffered formalin and routinely processed, and 3-μm sections were stained with haematoxylin and eosin.

Immunostaining was performed using Ventana BenchMark® *XT* according to the manufacturer's instructions, using appropriate antigen retrieval or hybridization steps and appropriate external controls. Details of the antibodies are provided in Table 1. Double immunostains were performed for selected antibody pairs.

DNA was extracted from two paraffin blocks, and PCR amplification of T cell receptor (TCR) beta and gamma gene rearrangements was performed using BIOMED-2 primers. PCR products were separated by capillary electrophoresis, and electropherograms were analysed by GeneScan (ABI3500). Unfortunately, insufficient amplification products were generated for assessment, likely due to degraded DNA quality.

Pathological findings

The mediastinal mass was received fresh and measured 60×40×25 mm. It was well circumscribed and had a homogeneous yellow-tan cut surface. Histologically, there was a large heterogeneous lymphoid mass adjacent to a separate normal small lymph node. The mass was traversed by bands of paucicellular fibrous tissue containing large blood vessels. No lymph node sinuses were apparent. No thymic tissue was present, which was confirmed by the complete absence of keratin immunostaining performed on sections from multiple paraffin blocks.

Table 1 Details of the antibodies used in this study

Antibody	Source/product	Clone	Dilution
Cytokeratin and epithelial markers (all negative, no evidence to suggest thymic tissue)			
AE1/AE3	Dako M3515	AE1/AE3	1:400
CK7	Dako M7018	OVTL-12/30	1:300
CK20	Dako M7019	KS20-8	1:500
CK14	Leica	NCL-L-11002	1:50
CK8/18	Cell Marque	818 M-96	1:300
CK19	Dako MO888	RCIC108	1:75
EMA	Dako M0613	E29	1:800
T-lymphoblast population markers positive			
CD3	Dako A0452	Polyclonal	1:600
CD2	Leica	NCL-L-CD2-271	1:50
CD5	Leica	NCL-L-CD5-4C7	1:200
CD7	Cell Marque	107 M-28 MRQ-56	Neat
CD4	Cell Marque	104R-18 SP35	Neat
CD8	Dako M7103	CD8/144B	1:50
TDT	Leica	NCL-L-TDT-339	1:80
CD1a	Leica	NCL-L-CD1A-235	1:50
CD99	Dako M3601	12E7	1:300
CD10	Leica	NCL-L-CD10 270	1:100
Follicular dendritic cell markers			
CD21	Neomarkers	M5-1086-5 269	1:50
CD35	Leica	NCL-CD35	1:50
Mantle zone B cells within FDC networks			
CD23	Cell Marque	123R-18 SP23	Neat
IgM	Dako A0426	Polyclonal	1:2,000
IgD	Dako A0093	Polyclonal	1:300
Plasmacytoid dendritic cell markers			
CD303	Dendritics DDX0043	124B3.13	1:800
CD2AP	Santa Cruz	SC-25272 B-4	1:50
Vascular, smooth muscle and lymphatic markers			
CD34	Dako M7165	QBEND10	1:100
CD31	Dako M0823	JC70A	1:150
D2-40	Covance	S16-3730-1000	1:40
Pan-actin	Dako M0635	HHF35	1:1,200
Vimentin	Dako M0725	V9	1:2,000
Smooth muscle actin	Dako M0851	1A4	1:1,500
Smooth muscle myosin	Dako M3558	SMMS-1	1:800
Calponin	Dako M3556	CALP	1:800
Desmin	Dako M0760	D33	1:800
Miscellaneous other markers (as described in the text)			
CD20	Dako M0755	L26	1:400
BCL6	Leica	NCL-L-bcl6 564	1:100
MIB1	Dako M7240	MIB1	1:400
CD163	Leica	NCL-L-CD163	1:100
EBER (ISH)	Ventana	(probe)	Neat
HHV-8	Leica NCL-HHV8-LNA	13B10	1:30
IgG	Dako A0423	Polyclonal	1:2,000
IgG4	Santa Cruz SC-69919	5C3	1:50
CD138	Dako M7228	ML15	1:50

Table 1 (continued)

Antibody	Source/product	Clone	Dilution
Kappa	Dako A0191	Polyclonal	1:12,000
Lambda	Dako A0193	Polyclonal	1:9,000

Three separate elements could be appreciated within the mass (Fig. 1):

1. HVCD component

   For the most part, the mass showed typical features of HVCD, stroma-rich variant. Scattered lymphoid follicles were traversed by radially penetrating arterioles. The follicles had regressed germinal centres with compact dense networks of FDCs and few residual BCL6+ germinal centre cells and were surrounded by expanded concentric layers of mantle zone lymphocytes. This follicular component was overshadowed by a markedly expanded interfollicular compartment rich in arborising hyalinised vessels and high endothelial venules surrounded by proliferating spindle cells expressing alpha-smooth muscle actin and vimentin. In the background were small lymphocytes, scattered histiocytes, moderate numbers of plasma cells often concentrated adjacent to fibrous septa and prominent clusters and dispersed CD2AP+ and CD303+ plasmacytoid dendritic cells (PDCs). Only rare small lymphocytes were EBER positive, whilst there was no HHV-8 staining.
2. T-lymphoblastic element

   The second component consisted of multiple relatively discrete foci of uniform T-lymphoblastic proliferation (Fig. 2) in the absence of any thymic epithelium. Whilst relatively well demarcated from the HVCD, there was loose intermingling of the two elements at their interface. The lymphoblastoid cells were small to intermediate in size and showed relatively little nuclear pleomorphism. Mitotic figures were numerous. The immunophenotype of the lymphoblastoid cells was consistent with a common thymocyte stage of T cell differentiation [19, 20], being TdT+, CD1a+, CD2+, CD3+, CD4+, CD5+ (approximately 70 %), CD7+, CD8+, CD10+ (approximately 40 %), CD34− and CD99+. The MIB1 proliferation index was approximately 70 %. Interestingly, within these T-lymphoblastoid zones were prominent numbers of PDCs (CD2AP+, CD303+) and polyclonal plasma cells, in addition to dispersed plump CD68+ histiocytes.

   Flow cytometry showed a predominance of T cells (83 % CD5+ and 58 % CD3+), with co-expression of CD4+ (69 %) and CD8+ (66 %); only a limited T cell panel was investigated. There were 14 % CD19+ B cells without a monoclonal population present. Cytogenetic analysis revealed a normal male karyotype.

   TCR gene rearrangement studies which were performed on DNA extracted from two paraffin blocks were unsuccessful owing to DNA degradation.

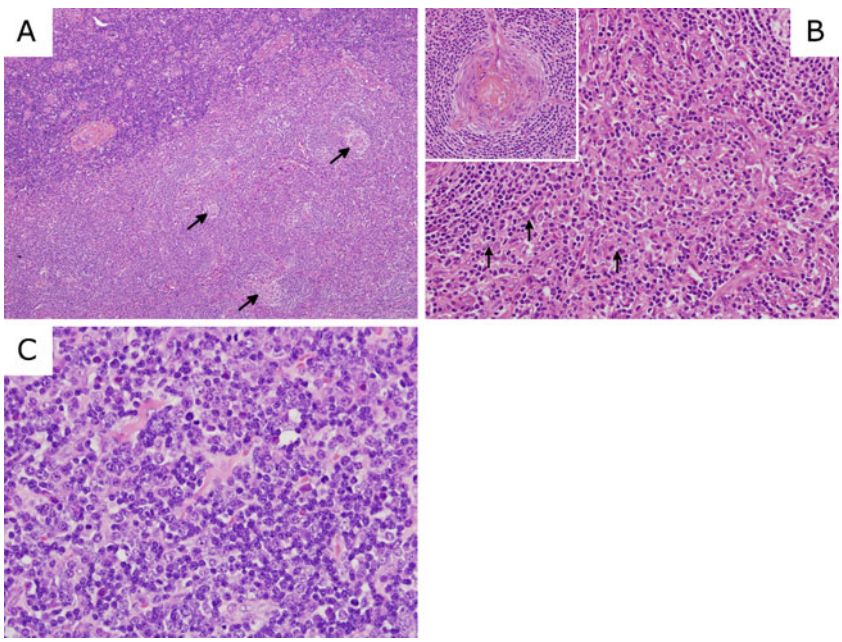

Fig. 1 **a** The T-lymphoblast proliferation (*upper left*) is sharply demarcated from HVCD (*lower right*) showing atretic follicles (*arrows*) and expanded interfollicular zone (H&E, ×10). **b** Interfollicular zone in HVCD component showing vessels and follicular dendritic cells (*arrows*). The *inset* shows atretic follicle with radial hyalinised arterioles, layered FDC network and concentric mantle zone lymphocytes (H&E, ×40). **c** High-power T-lymphoblast proliferation, also containing mature plasma cells (H&E, ×60)

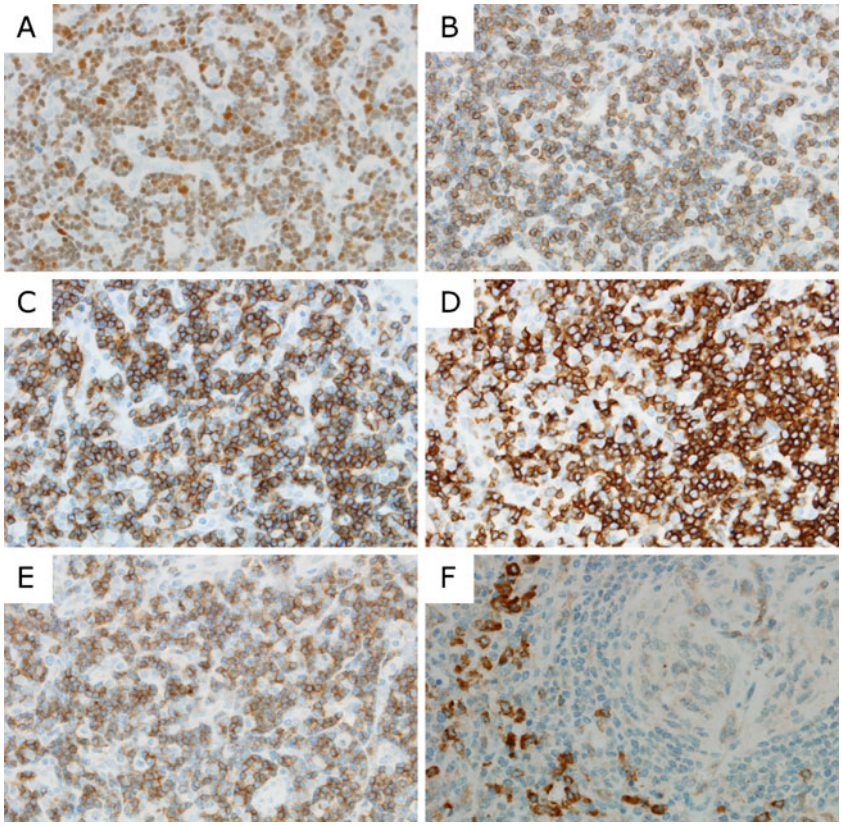

Fig. 2 Lymphoblast proliferation immunophenotype (**a** TDT, **b** CD3, **c** CD4, **d** CD8, **e** CD1a) and **f** CD2AP highlights plasmacytoid dendritic cells adjacent to an atretic follicle (×60)

3. FDC proliferation

The third component consisted of swirling and fascicular arrangements of proliferating FDCs (Fig. 3), as confirmed by staining for CD21 and CD35. Whilst striking in extent, the FDC proliferation nevertheless maintained a compartmentalised or 'organoid' appearance at low power. In many areas, these swirling sheets of FDCs appeared to originate from regressed follicle centres where tight concentric FDC arrangements were present at their core. The proliferating FDCs were always accompanied by expanded and distorted mantle zones, as confirmed by double immunostains which showed the colocalization and intimate admixture of the FDCs with CD23+, IgM+ and IgD+ mantle zone cells. The FDCs were largely spindled in morphology, lacked atypia, were without significant mitotic activity and had a very low proliferation (MIB1) index of estimated <2 %. Despite the widespread nature of this FDC proliferation throughout the HVCD component, there was no infiltration beyond the native microenvironment, nowhere was there any frank mass-forming or sheet-like proliferation of these FDCs and there was no destruction of underlying architecture.

Discussion

The two issues of interest in this unique case of HVCD relate to the nature and significance of the multifocal T-lymphoblastoid proliferation and the striking 'organoid' FDC proliferation.

The T-lymphoblastoid element had an immunophenotype corresponding to the common thymocyte stage of cortical thymocyte differentiation [19, 20]. In the absence of any thymic epithelial elements to suggest entrapped normal thymus, this finding is usually strongly indicative of a pathological proliferation of T lymphoblasts. Whether in this case the population represents a hyperplastic, heterotopic/choristomatous or neoplastic proliferation (T-lymphoblastic lymphoma) remains unclear. Rare case reports and a recent case series [17] support the concept of an indolent T-lymphoblastic proliferation, although the origin of non-lymphomatous immature T cells outside the thymus remains obscure. In contrast to a reported case of FDC sarcoma and immature T cell proliferation [16], in which infiltrating immature T cells were admixed with atypical follicular dendritic sarcoma cells, in our case the T-lymphoblastic population formed multiple discrete aggregates between the compartmentalised expansile FDC nodules. There was no admixture of the two cell types and no significant disruption of architecture by either cell population. The

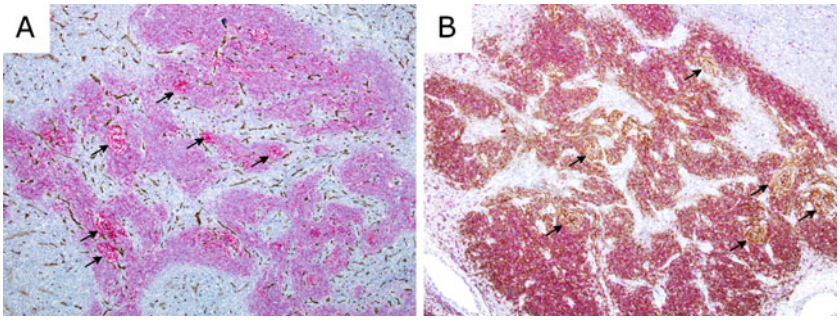

Fig. 3 **a** Combined CD34 (*brown*) and CD35 (*red*) immunostains showing expanded FDC network around atretic follicles (*arrows*) (×10). **b** Combined CD35 (*brown*) and IgD (*red*) immunostains showing mantle zone B cells within expanded FDC networks around atretic follicles (*arrows*) (×10)

presence of tumour-like aggregates of T lymphoblasts has been noted in two cases of CD with follicular dendritic cell tumour in the recent cases series [17], with all other aggregations being patchy in distribution. The microenvironment in which the T lymphoblasts proliferate in this case includes small CD31+ venules, PDCs, polyclonal plasma cells and larger CD68+ histiocytes. Plasmacytoid dendritic cells and polyclonal plasma cells would be unusual in typical cases of T-lymphoblastic lymphoma; thus, their presence might argue that the T-lymphoblastic proliferation is non-neoplastic.

In our case, owing to degraded DNA (*ex* paraffin-embedded material), we could not determine whether the T lymphoblasts are monoclonal or polyclonal heterotopic collections. It should be noted that all previous reports of indolent T-lymphoblastic proliferations outside the thymus have lacked monoclonality [12–18]. One may speculate that a microenvironment may exist whereby circulating T progenitors are entrapped and become T lineage-committed outside the normal thymic microenvironment. Early studies into the pathogenesis of CD demonstrated overexpression of inducible adhesion molecules including vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) [21]. Within the normal thymus, intimate contact with VCAM-1-positive stroma is required for migration of double-negative (subcapsular zone) thymic lymphocytes. Subsequently, double-positive (cortical) thymocytes no longer require contact with stromal VCAM-1, although they undergo positive selection under the influence of ICAM-1 stromal signalling [19, 20]. It could be proposed that in this instance of HVCD, an alteration in the microenvironment, including altered stromal signalling, may have lead to the attraction of T progenitors and positive selection recapitulating T cell differentiation in the thymic cortical microenvironment.

Plasmacytoid dendritic cells are implicated in a wide variety of immune functions. These cells respond to a variety of DNA and RNA viruses by secreting copious amounts of interferon-α and to a lesser extent other cytokines including IL-6, IL-8 and TNF-β [22]. Interleukin-6 in particular is postulated to drive CD via a dysfunctional local cytokine network [11]. The presence of PDCs adjacent to areas of T-lymphoblastic proliferation raises the possibility that a local cytokine milieu mediated by PDCs may be responsible for these T-lymphoblastic expansions, though to our knowledge the presence of significant PDCs has not been studied in other cases of reported indolent T-lymphoblastic expansions. Although the pathogenesis underlying Castleman lymphadenopathy remains poorly understood, recent models emphasise the role of the virus HHV-8 in some cases, whilst an unidentified viral agent with lower pathogenicity may be relevant in cases lacking HHV-8 infection [11].

The second component of interest in this case is the organoid proliferation of follicular dendritic cells. FDCs have been implicated in the pathogenesis of CD. A recent publication suggests that in multicentric CD, FDCs may drive disease by presenting an HHV-8-associated antigen [23]. HVCD has been associated with FDC abnormalities shared by FDC sarcoma including overexpression of EGFR [3]. Whilst stroma-rich changes may characterise some forms of HVCD, there are no clear criteria to distinguish between FDC hyperplasia and FDC sarcoma, and it is conceivable that an "in situ" form of FDC sarcoma may exist. Sequential biopsies from a reported case of FDC sarcoma arising in HVCD showed an initially expansile growth of FDC networks without architectural disruption or cellular atypia [8], somewhat similar to the changes in our case. A recent publication describes folliculocentric B cell-rich FDC sarcoma [24], but the morphology described, which in particular includes cellular atypia, sheet-like overgrowth and loss of some FDC markers, is quite distinct from our case. The issue of FDC dysplasia and distinction from FDC hyperplasia is difficult, particularly in the setting of HVCD [25]. In our case, mantle zone B cells remained closely admixed with

the expanded FDC networks and the FDC proliferation remained compartmentalised in nature and also lacked destructive or sheet-like overgrowth. Furthermore, there was no nuclear atypia and the proliferation index was extremely low. Collectively, these features strongly favour florid FDC hyperplasia rather than FDC sarcoma.

The final intriguing aspect of this case is the strong probability of a familial predisposition to HVCD. The patient's mother and aunt have had histologically confirmed HVCD diagnosed more than 10 years ago, although the original diagnostic material is not available for our review. This possible familial association would be a unique occurrence as, to our knowledge, an inherited predisposition to CD has not been previously described.

In summary, we report a patient with HVCD in the context of a possible underlying familial predisposition and the lesion complicated by multifocal T-lymphoblastic and florid FDC proliferation, both latter components were most likely benign in nature. The pathogenesis of CD, as currently understood, suggests that there may be an underlying inherited subtle immune dysfunction in this patient's family. One may speculate that in a dysregulated immunological environment, an unknown infectious agent or agents have led to the development of HVCD. Subsequently, a microenvironment mimicking the normal thymic cortex, and an inappropriate cytokine milieu possibly facilitated by accumulations of PDCs, may have resulted in the interesting combination of an indolent T-lymphoblastic proliferation and the striking FDC overgrowth. At most recent follow-up, 30 months after biopsy, the patient remains disease free, and whilst he should be followed closely, the long-term outlook we suggest should be guardedly optimistic, with little likelihood of progression to T-lymphoblastic lymphoma or follicular dendritic sarcoma.

Conflict of interest The authors have no connection or financial relationship to any organisation or product mentioned in the article.

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