A Colonization of a Different Kind

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Abstract An unusual morphological pattern in the lymph node can at times, pose a diagnostic problem. We report a case of a 55 year old male whose cervical lymph node biopsy showed an unusual pattern of follicular colonization by T-lymphoblasts. The interfollicular area showed a diffuse infiltrate of Langerhans cells. A diagnosis of a T lymphoblastic lymphoma coexisting with Langerhans cell histiocytosis like lesion was made, keeping in mind lack of clinical evidence for the latter.

Keywords Follicular colonization · T lymphoblastic lymphoma · LCH like lesion

Introduction

Morphological patterns described in lymphoblastic lymphomas are commonly a diffuse infiltrative pattern, Indian file pattern or a starry sky pattern [1]. Lymphoblastic lymphoma showing colonization of follicular centre cells is an unusual pattern and to our knowledge, has not yet been described in literature. In addition, only four cases of composite T-LL with LCH have so far been described in

literature [2–4]. Abnormal proliferations of Langerhans cells (LCs) histologically indistinguishable from true LCH may be seen concurrently with a malignancy. It is possible that, in some instances, the presence of dual pathologies is coincidental and both are true neoplasms; however, the lack of evidence for LCH elsewhere is most supportive of an exaggerated reactive phenomenon and are better described by the term LCH like lesion [2].

Case Report

A 55 year old male, farmer by profession, presented with cervical and axillary lymphadenopathy of 5 months duration. He had no accompanying B symptoms. Besides the fact that he was a known diabetic and hypertensive on treatment, his general health was good. His blood picture was as follows, Hb = 14.1 gm %, total leukocyte count = 8,600 cells/mm³ and platelet count = 291×10^6 /L. His peripheral smear, bone marrow aspirate and trephine were within normal limits. CT scan chest revealed multiple axillary, cervical and small mediastinal lymph nodes. Largest in size was the right axillary lymph node measuring 2.8×2.1 cm. CT scan abdomen showed mild hepatomegaly with fatty infiltration. No splenomegaly or retroperitoneal nodes were seen. His cervical lymph node was biopsied. Sections from lymph node showed a neoplasm composed of scattered follicles showing colonization by a uniform population of atypical/immature lymphoid cells (Fig. 1a). The cells within the follicle were unlike the twisted or angulated nuclei that are classical of follicular centre cells. The cells colonizing the follicles had scanty cytoplasm, round nuclei with immature chromatin (Figs. 1b, and 2a). The interfollicular area and sinuses showed diffuse infiltration by elongated histiocytes with grooved nuclei (Fig. 2b). On immunohistochemistry, the tumour cells

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Fig. 1 **a** H&Ex100 follicular pattern of lymphoblasts. Interfollicular pale areas show sheets of langerhans cells. **b** H&Ex200 follicular colonization by lymphoblasts

colonizing the follicles were found to be CD3 positive, CD5 positive, CD7 positive, CD34 positive, TdT positive, CD20 negative and CD10 negative. CD23 staining highlighted the residual follicular dendritic cell network. The interfollicular infiltrate of histiocytes were positive for CD68, S-100 and CD1a (Fig. 3a, b, c, d, e, f). In the absence of clinical evidence of LCH, a diagnosis of T Lymphoblastic Lymphoma coexisting with an LCH-like lesion was made. The patient was then lost to follow up citing personal reasons for a period of 6 months, after which he reported back. On re-evaluation, he had a huge bulky lymphnodal mass in the left axilla measuring 15×10 cm. His peripheral smear and bone marrow studies were within normal limits. An ultrasound abdomen, skeletal survey and bone scan were done, which were normal. The patient was then started on BFM (Berlin- Frankfurt-Munster)-90 protocol for lymphoblastic lymphoma. After the first cycle of induction chemotherapy, a CT scan thorax was done to look for any residual disease. Multiple enlarged lymph nodes were seen in the left axilla, largest measuring 4.3×2.8 cm, some of them showing necrosis (Fig 4). Multiple enlarged lymph

Fig. 2 **a** H&Ex400 lymphoblasts with scanty cytoplasm, round nuclei, immature chromatin within the follicle. **b** H&Ex1000 elongated histiocytes with grooved nuclei (Langerhans cells)

nodes were also seen in the cervical and supraclavicular region, largest measuring 2.8×1.9 cm. In view of residual disease, the patient was started on Phase 2 induction chemotherapy and is currently undergoing the same.

Discussion

A follicular pattern resulting from follicular colonization of neoplastic cells has been classically described in mantle cell lymphoma and marginal zone lymphoma. In mantle cell lymphoma, the neoplastic mantle cells either grow outwards to produce a mantle zone pattern or grow inward into the benign follicular centre cells, resulting in a pattern that can mimic a true follicular pattern [5, 6]. In marginal zone lymphomas the neoplastic cells are of medium size and have abundant clear cytoplasm. These are seen to invade the follicular centre cell compartment (colonization), with a resulting pattern that may be indistinguishable from a true follicular pattern [6]. Such a pattern has not been described in

Fig. 3 **a** IHCx200 CD7 positive lymphoblasts within the follicle. **b** IHCx200 CD23 staining highlights the residual follicular dendritic cell network. **c** IHCx200 lymphoblasts are CD34 positive. **d** IHCx200

lymphoblasts are TdT positive. **e** IHCx200 langerhans cells are S100 positive. **f** IHCx400 langerhans cells are CD1a positive

lymphoblastic lymphoma so far in literature. By convention, the term lymphoblastic lymphoma is used to designate a patient with lymph node or extranodal site based disease with no or minimal evidence of peripheral blood and bone marrow involvement [7]. Lymphoblastic lymphomas classically

exhibit a diffuse aggressive pattern of infiltration. In the majority of instances, the neoplastic cells completely efface the lymph node architecture, invade the capsule and show extensive crush artefact. The neoplastic cells characteristically split the pericapsular collagen fibres producing the

Fig. 4 Post contrast axial CT sections of the chest showing extensive necrotic left axillary adenopathy

classical Indian-file pattern. In about one third of cases, lymphoblasts selectively involve the interfollicular and paracortical zones, leaving residual ‘naked’ germinal centres. A starry sky pattern caused by the presence of interspersed macrophages may be present focally but is only infrequently as diffuse and prominent as in Burkitt’s lymphoma. In some biopsy specimens, the neoplasm can be subdivided into nodules by strands of collagen, resulting in a pseudonodular pattern. This should not be misinterpreted as follicle formation [1].

The term LCH encompasses a rare group of disorders characterized by an accumulation or proliferation of abnormal Langerhans cells (LCs). As with normal LCs, the neoplastic LCs consistently express CD1a and S-100 protein. Its clinical spectrum is wide, ranging from an indolent isolated lesion to a rarer life-threatening multisystem disease commonly involving bone marrow, lymphatics, skin, liver, lung, and spleen [8]. LCH has been described in association with a variety of other tumor types, preceding, after, or synchronous with the other tumor. The most common associations are with malignant lymphoma and leukemia [8, 9]. Although CD1a can be useful in the assessment of Langerhans-cell differentiation, this marker is expressed in cortical thymocytes and is frequently positive in precursor T-lymphoblastic leukaemia/lymphoma [7, 10]. Kanter and co-workers [10, 11] proposed a biological association between Langerhans-cell histiocytosis and acute lymphoblastic leukaemia in 1976, but considered this link unlikely on the basis of pluripotent-stem-cell theory as it was understood at that time. Studies of mice by Anjuère and colleagues [10, 12], in which Langerhans cells were generated *in vivo* from lymphoid-committed CD4^{low} precursors and CD44⁺/CD25⁺ pro-T cell precursors, suggest that Langerhans cells might derive from the lymphoid lineage. Feldman et al. reported two cases of langerhans-cell

histiocytosis, one seen synchronously and one arising 2 years after the initial diagnosis of precursor T-lymphoblastic leukaemia/lymphoma. The Langerhans-cell histiocytosis cells and the precursor T lymphoblastic leukaemia/lymphoma cells had identical rearrangements of the gene for T-cell receptor, confirming a clonal relation between the two neoplastic diseases. The presence of a common stem cell suggests a state of primitive differentiation, in which rearrangement of the gene for T-cell-receptor precedes commitment to a T-cell or Langerhans-cell lineage. The existence of such a precursor is unlikely because most neoplasms of Langerhans cells do not have rearrangements of the T-cell-receptor genes [10]. The possibility of lineage switching is supported by recent data that showed differentiated B cells could be reprogrammed immunophenotypically and functionally into macrophages [10, 13]. Chemotherapy might kill all cells with lymphoblastic differentiation, whereas cells of the same clone that preferentially show histiocytic differentiation might be more chemoresistant and survive to present later as histiocytic neoplasms [10, 14]. Schmitt-Graeff et al. [15] describe a concomitant occurrence of LCH and a myeloid sarcoma (MS) characterized by the presence of the same chromosomal aberration (trisomy 8) in both populations. The rising evidence for lineage plasticity in hematopoietic neoplasms suggests a possible biological relation between precursor T-lymphoblastic leukaemia/lymphoma and Langerhans-cell histiocytosis in the same individual.

A study by Lesley J et al. [2] report the rare occurrence of an LCH-like lesion occurring concurrently in a lymph node also harboring T-LL, and describe for the first time similar lesions in skin affected by mycosis fungoides, lymphomatoid papulosis and cutaneous B-cell pseudo-lymphoma. They observed that in literature, such lesions are often labeled as LCH. They put forth the concept that this term is misleading given the lack of clinical evidence that these lesions follow an aggressive course and substantiated this argument with clonal studies in two of their cases. The clonality of the LC proliferation was assessed using laser capture microdissection and the human androgen receptor assay and these lesions were found to be polyclonal. This suggests that, at least in a proportion of cases, the aggregates of LCs occasionally identified within other lymphoproliferative lesions may represent a reactive proliferation rather than a potentially aggressive second neoplasm [2]. In light of these observations, it seems likely that in a significant proportion of cases, these lesions are reactive cytokine-mediated proliferations, as suggested by Egeler et al. [8]. Therefore, in the interim, without knowledge of clonal status, it may be appropriate to adopt, as these authors have, the somewhat looser but perhaps more accurate terminology, LCH-like lesion [2].

In summary, we report the rare occurrence of an LCH-like lesion occurring concurrently in a lymph node

harbouring a T lymphoblastic lymphoma. The lack of evidence for LCH progression or disease elsewhere strongly supports the concept that they may represent a reactive phenomenon. This case also demonstrates an unusual histological pattern of follicular colonization by lymphoblasts. To the untrained eye, on morphology alone, this may mimic a follicular lymphoma.

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