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CORRESPONDENCE

Interdigitating dendritic cell sarcoma: diagnostic pitfalls, treatment challenges and role of transdifferentation in pathogenesis

Sir,

We report the case of a 49-year-old gentleman presenting with rapidly enlarging, cervical lymphadenopathy diagnosed with interdigitating dendritic cell sarcoma (IDCS). We describe the diagnostic pitfalls and treatment challenges of this rare dendritic cell (DC) neoplasm and explore the role of tumour cell transdifferentiation in its pathogenesis.

Our patient had a history of traumatic splenectomy and an extra-adrenal paraganglioma managed with complete surgical excision several years prior. He presented with rapidly enlarging cervical lymphadenopathy but was otherwise asymptomatic. A core biopsy showed clusters of atypical lymphohistiocytic proliferation with a number of large epithelioid cells and admixed predominance of small T cells with occasional clusters of small B cells confirmed to be monoclonal CD5+ B cells on flow cytometry. Given difficulty reconciling the histological, immunohistochemical and flow features with a unifying diagnosis, an excisional biopsy was performed showing sheets of histiocytic cells on a background of small lymphocytes (Fig. 1). The histiocytic cells had a large, cleaved and folded nucleus with moderate amount of eosinophilic cytoplasm; they were S100, CD68, vimentin and fascin positive and negative for CD1a, CD21 and CD35. Negative staining for chromogranin and synaptophysin with normal normetadrenaline levels excluded recurrent paraganglioma, a tumour which is usually S100 positive. Melanoma and carcinoma were excluded with negative staining for Melan A and AE1/AE3, respectively. The majority of admixed small lymphocytes were CD3+ T cells with occasional clusters of B cells; Ki-67 was estimated at 60%. Flow cytometry of sampled tissue identified a B cell population with an immunophenotype consistent with chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL). In combination, these features were in keeping with a diagnosis of a DC neoplasm, most consistent with IDCS, on the background of SLL.

Staging was completed with a bone marrow biopsy demonstrating involvement by SLL only and positron emission tomography-computed tomography (PET-CT) imaging showing a bulky cervical node conglomerate with intense FDG avidity (SUV_{max} 27) in addition to numerous, less avid nodal clusters in both cervical chains, axillae, the palatine tonsils and the retroperitoneum. Treatment was commenced with CHOP chemotherapy, though after two cycles the patient developed B symptoms with progressive lymphadenopathy and multifocal FDG-avidity on PET-CT with especially bulky retroperitoneal disease. Excisional biopsy of a cervical node at this time confirmed presence of composite neoplasm with a predominance of IDCS, areas of necrosis and small volume SLL.

Second line treatment with gemcitabine/docetaxel was commenced with prompt resolution of B symptoms and interim imaging after two cycles was consistent with a partial metabolic response. Autologous haemopoietic progenitor cell mobilisation and collection as well as HLA-typing of siblings were organised in case either type of stem cell transplantation was a potential future treatment option. However, end of treatment imaging demonstrated disease progression with increase in size and intensity of retroperitoneal and mediastinal nodes. Recurrence of B symptoms, severe abdominal discomfort, pleural effusions and ascites quickly followed. At this stage the patient was too unwell to proceed with further salvage or high dose chemotherapy and died 10 months after the initial diagnosis of IDCS.

Dendritic cells are the immune system's accessory cells, functioning as the key antigen presenters and initiators of an immune response. Langerhans, plasmacytoid and interdigitating dendritic cells (IDCs) are derived from a common myeloid haemopoietic progenitor while follicular dendritic cells (FDCs) and fibroblastic reticulum cells are derived from a mesenchymal stem cell. The World Health Organization (WHO) classifies DC neoplasms, which account for <1% of lymphoid neoplasms, as myeloid-derived histiocytic neoplasms (histiocytic sarcoma), myeloid-derived dendritic neoplasms (Langerhans cell histiocytosis and sarcoma, IDCS, and indeterminate and plasmacytoid DC tumours) and stromally derived follicular dendritic cell sarcoma (FDCS).[1] A systematic review on the topic of dendritic cell neoplasms published in 2013 reported on 100 cases of IDCS[2] and while further reports have been published, including institutional case reviews,[3] the paucity of literature on this entity highlights its rarity and potentially the under-reporting and/or under-recognition of this at times difficult to diagnose malignancy.

The median age at diagnosis is 56.5 years with a slight male predominance. The vast majority present with otherwise asymptomatic lymphadenopathy while constitutional symptoms are commonly observed in patients with widespread disease. Extranodal disease is seen in 30% while bone marrow involvement is seen in 11% of cases. Unlike other DC neoplasms, prognosis is different for patients with localised and systemic disease, the 2 year overall survival being 68.5% and 15.8%, respectively. Median survival in patients with systemic disease is 9 months and factors on univariate analysis found to be predictive of poor outcome include young age (≤40 years), intra-abdominal disease and extra-nodal involvement.[2]

Histopathologically, IDCS is characterised by diffuse infiltration by pleomorphic spindle cells with occasionally prominent nucleoli and abundant eosinophilic cytoplasm, arranged in whorled clusters in a storiform pattern.[4] Effacement of the entire node is seen occasionally but generally a paracortical distribution with preserved surrounding lymphoid follicles is observed. Occasional Reed–Sternberg-like cells are seen, while the majority of admixed lymphocytes are T cells with necrosis present in 41% of cases. These features can be indistinguishable from other dendritic cell neoplasms and assessment with markers including CD68, lysozyme, CD1a, CD21, CD35, vimentin, fascin and S100 is essential. In general, S100 is universally expressed, with CD68 and lysozyme seen in 50% and 25%, respectively, while CD1a is generally absent. CD1a and langerin positivity

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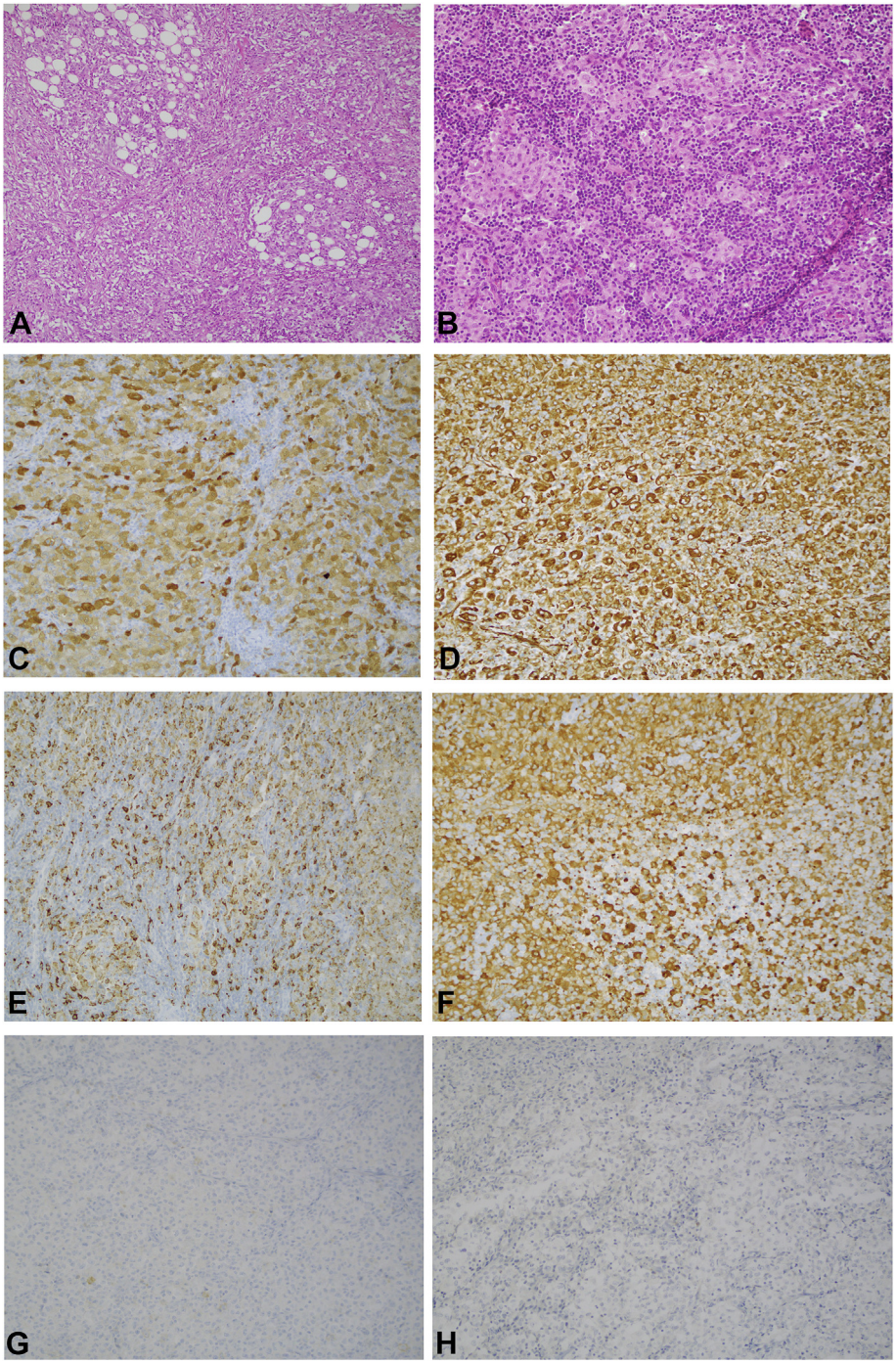

Fig. 1 Lymph node biopsy with histological and immunohistochemical features of interdigitating dendritic cell sarcoma. (A,B) Pleomorphic spindle cells with prominent nucleoli and eosinophilic cytoplasm forming clusters in storiform pattern with admixed lymphocytes (H&E). (C−H) Immunohistochemistry consistent with IDCS including (C) S100 positive, (D) vimentin positive, (E) CD68 positive, (F) fascin positive, (G) CD1a negative and (H) CD21 negative.

is suggestive of tumours derived from Langerhans cells while CD21 and CD35 are expressed by FDCS. Ki-67 expression is low in most cases, though more aggressive proliferation, as in our case, has been reported. Therefore, making a diagnosis of IDCS can be difficult and commonly missed, with as many as 11% of reported cases given an alternative diagnosis initially. IDCS should be considered as a differential to spindle cell carcinoma, melanoma, anaplastic large cell lymphoma, peripheral nerve sheath tumour, mesenchymal and other types of dendritic cell neoplasms.

Interestingly, in a substantial number of cases (9−17%) there is a past or concurrent history of haematological or solid organ malignancy. A history of CLL/SLL or synchronous presentation with CLL/SLL and IDCS is commonly reported with some groups proving a clonal relationship between the two neoplasms.[5–7] Fraser *et al.* demonstrated identical V-J junction sequence and trisomy 12 in both tumours with additional cytogenetic abnormalities seen in the IDCS only, suggesting that clonal evolution of the mature low grade B cell lymphoma lead to transformation via a process of

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