Interdigitating dendritic cell sarcoma of salivary gland associated lymphoid tissue not associated with HHV-8 or EBV infection

N Barwell, R Howatson, R Jackson, A Johnson, R F Jarrett, G Cook

**CASE REPORT**

Interdigitating dendritic cell sarcoma (IDCS) is an extremely rare malignancy derived from professional antigen presenting cells. This report describes a case of IDCS arising in the salivary gland associated lymphoid tissue of the parotid gland of a 51 year woman, presenting with a painless neck swelling. Histologically, sheets of S100+/CD68+/CD45+/CD34+/CD1a+ spindle cells were surrounded with an inflammatory infiltrate with no evidence of B or T cell clonal proliferations. No evidence of either human herpesvirus 8 or Epstein-Barr virus could be detected by quantitative polymerase chain reaction in the tumour cells with serological evidence of previous Epstein-Barr virus infection. The patient remains well and disease free 24 months after presentation without specific treatment.

Dendritic cells are professional antigen presenting cells that play a pivotal role in orchestrating both the innate and adaptive immune responses.1 Dendritic cells are a heterogeneous group of cells that includes Langerhans' cells, dermal dendrocytes, follicular dendritic cells (FDCs), and interdigitating dendritic cells (IDCs). IDCs are primarily located in the T cell areas of lymphoid tissue (lymph nodes, thymic medulla, and spleen) and are responsible for major histocompatibility complex restricted stimulation of resting T cells.2 IDC tumours (IDC sarcoma; IDCS) are extremely rare, generally occurring in lymph nodes, although splenic involvement has been reported.1 The aetiology of IDCS is not known, although a viral aetiology (Epstein-Barr virus [EBV] and human herpesvirus 8 [HHV-8]) has been suggested in the development of the closely related FDC sarcoma.1,2 Here, we report a case of IDCS arising from the salivary gland associated lymphoid tissue of the parotid gland that demonstrates no association with either EBV or HHV-8.

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**PATHOLOGICAL FINDINGS**

The resected lymph node showed reactive changes only. The resected deep lobe of the parotid gland revealed a well circumscribed white lesion (25 × 12 mm) on sectioning. Histological examination demonstrated preserved lymphoid architecture, with reactive follicular and paracortical hyperplasia around an ill defined nodule, consisting of a proliferation of large spindle shaped cells with large oval/round nuclei, prominent nucleoli, and occasional mitotic figures, arranged in sheets with no specific architectural features (fig 2). There was a large reactive infiltrate consisting of macrophages, granulocytes, and occasional plasma cells. The spindle cells stained positively for S100, CD68, and CD45 (Dako, Ely, Cambridgeshire, UK) but did not stain with CD1a (Immunotech/Coulter, UK), CD34 (Serotec, Oxford, UK), CD3 (Dako), or CD20 (Dako). There was no demonstrable evidence of clonal B or T cell proliferation, as determined by polymerase chain reaction (PCR) assessment of immunoglobulin heavy (IgH) chain and T cell receptor (TCR) gene rearrangements.

Quantitative PCR using TaqMan® methodology was used to detect EBV and HHV-8 genomes, as described previously.3 Positive controls comprised DNA from the EBV positive Raji and the HHV-8 positive BCP-1 cell lines, with negative controls comprising water in place of template DNA. A β globin TaqMan™ assay was used to confirm that sufficient amplifiable DNA was present within the tumour samples. No evidence of EBV or HHV-8 viral genomes was found in the biopsy material examined (fig 3). EBV and cytomegalovirus serology were consistent with previous infection.

**DISCUSSION**

In our present case study we analysed a tumour arising in the salivary gland associated lymphoid tissue that showed morphological and immunohistochemical features of IDCS. To date, 32 cases of IDCS have been reported, including this one. IDCs are extremely rare and generally occurs in adults.
(median age, 51 years; range, 13–86), with a male predominance (male to female ratio 19 : 13). Most reported cases of IDCS have presented in lymph nodes, although extranodal primary sites include the small intestine, nasopharynx, testis, skin, tonsil, and spleen, with secondary involvement of bone marrow, bone, liver, spleen, lung, ovary, and skin being reported occasionally. \(^{26}\)

Microscopically, the tumour cells are predominantly pleomorphic in shape, although occasionally, spindle shaped cells are seen. Immunohistochemical studies show that the tumour cells are positive for S-100 protein, CD45, HLA-DR, and CD68 but negative for B cell and T cell markers, CD30, CD1a, and complement receptors. \(^{2}\) Ultrastructurally, the tumour cells possess complex interdigitating cytoplasmic dendritic processes, and Birbeck granules are absent. The differential diagnosis includes undifferentiated metastatic carcinoma, malignant and Langerhans’ cell histiocytosis, anaplastic large cell lymphoma, primary and metastatic sarcoma, and malignant melanoma. The diagnosis of any one of these entities can rarely be reached from light microscopy alone, and immunohistochemical and ultrastructural studies can contribute to discriminating between them. Genetically, as illustrated in our case, there is no evidence of clonal IgH or TCR gene rearrangements.

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The aetiology of IDCS and the closely related FDC sarcoma remains unclear and a viral pathogenesis has previously been suggested. \(^{3,4}\) HHV-8 has been implicated in several malignant conditions. HHV-8 DNA sequences have been demonstrated in all the variants of multicentric Castleman’s disease and are tumour cells are positive for S-100 protein, CD45, HLA-DR, and CD68 but negative for B cell and T cell markers, CD30, CD1a, and complement receptors. \(^{2}\) Ultrastructurally, the tumour cells possess complex interdigitating cytoplasmic dendritic processes, and Birbeck granules are absent. The differential diagnosis includes undifferentiated metastatic carcinoma, malignant and Langerhans’ cell histiocytosis, anaplastic large cell lymphoma, primary and metastatic sarcoma, and malignant melanoma. The diagnosis of any one of these entities can rarely be reached from light microscopy alone, and immunohistochemical and ultrastructural studies can contribute to discriminating between them. Genetically, as illustrated in our case, there is no evidence of clonal IgH or TCR gene rearrangements.

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universally present in Kaposi's sarcoma. In multiple myeloma, HHV-8 was proposed to have a pathogenic role through infection of non-neoplastic bone marrow dendritic cells, although subsequent reports have not established a causal link between HHV-8 infection and plasma cell dyscrasias. We tested the hypothesis that HHV-8 may play a role in the pathogenesis of IDCS and, as demonstrated, there was no evidence of the presence of HHV-8 viral genomes.

These tumours may show a spectrum of biological behaviour, from low to high grade clinical courses with rapid progression to death in some patients. Follow up data, available for 26 patients in the literature, demonstrate a mean follow up time of 17.6 months: at six months, 10 patients had died from disease progression and two further patients had died of other causes. At the time of our case report, 14 patients were still alive, of whom eight were alive with disease and six were without disease. The median overall survival is 10 months. Response to treatment is generally poor and the most effective treatment and reliable prognostic factors remain unknown. The patient presented here had a more benign clinical course, with no evidence of disease recurrence at 24 months from presentation without specific treatment.

In conclusion, we present a case of IDCS arising in parotid gland associated lymphoid tissue characterised by the absence of clonal T and B cell proliferation that was not associated with HHV-8 infection.

**Authors’ affiliations**

N Barwell, G Cook, Department of Haematology, Monklands Hospital, Airdrie ML6 0JS, UK

R Howatson, Department of Pathology, Monklands Hospital

R Jackson, Department of Pathology, Glasgow Royal Infirmary, Glasgow C31 2ER, UK

A Johnson, Department of ENT Surgery, Monklands Hospital

R F Jarrett, LRF Virus Centre, University of Glasgow, Glasgow G61 1QH, UK

Correspondence to: Dr G Cook, Blood and Marrow Transplantation, Leeds Teaching Hospitals, St James’s University Hospital, Leeds LS9 7TF, UK; Gordon.Cook@leedsth.nhs.uk

Accepted for publication 19 May 2003

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