SHORT REPORT

Primary T cell lymphoma of salivary gland: a report of a case and review of the literature

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Lymphoma of the salivary gland accounts for 5% of cases of extranodal lymphoma and 10% of malignant salivary gland tumours. Most primary salivary gland lymphomas are B marginal zone lymphomas arising on a background of sialadenitis associated with autoimmune disorders such as Sjogren's syndrome. Primary T cell lymphoma of the salivary gland is rare. This report describes a case of primary T cell lymphoma arising in the parotid gland of an elderly white man, which was notable for its striking resemblance to a B cell extranodal marginal zone lymphoma. Immunohistochemistry and gene rearrangement studies confirmed the clonal T cell nature of the tumour. There was no molecular evidence of Epstein-Barr virus (EBV) infection of neoplastic or surrounding cells. Only 14 cases of primary T cell lymphoma of the salivary glands have been recorded in the literature, most being from the Orient and having extremely variable prognosis. Those with a T/natural killer cell phenotype are associated with EBV infection. This case highlights the fact that T cell lymphoma in the salivary gland can mimic closely the morphological features of B cell extranodal marginal zone lymphoma.

CASE REPORT

A 69 year old white man presented with an apparently isolated swelling on the left side of his neck that had become progressively more prominent over a period of several months. He was otherwise well. Clinical examination revealed a large mass that appeared to arise within the left parotid gland. There was no clinical or laboratory evidence of pre-existing autoimmune disease, enteropathy, or more extensive disease of the lymphoreticular system. The patient progressed to an incisional biopsy of the mass.

We received multiple pale fragments of tissue admixed with some adipose tissue measuring altogether 20 × 8 × 8 mm. Macroscopic examination revealed no specific features. Microscopy revealed salivary and adipose tissue widely infiltrated by a monotonous population of medium sized cells with cleaved nuclei and inconspicuous nucleoli. Frequent mitotic activity and apoptotic bodies were evident (fig 1A). Occasional groups of malignant cells were identified infiltrating ductal epithelium, the appearances being reminiscent of lymphoepithelial lesions of a low grade extranodal marginal zone non-Hodgkin's lymphoma (NHL) (fig 1B). However, immunohistochemical staining revealed that the neoplastic cells were positive for markers indicative of T cell lineage (CD3, CD5, CD43, and UCHL 1) (fig 1C,D) and negative for the B cell markers CD20 and CD79a (fig 1E). Sections stained for the natural killer (NK) cell marker CD56, CD30, ALK1 (anaplastic lymphoma kinase antibody), CD21, granzyme B, and TdT (terminal deoxynucleotidyl transferase) were negative. The features of the infiltrate were those of a T cell NHL, which also showed involvement of the surgical resection margins. There

was no evidence that the lymphoma had arisen within an intraparotid lymph node and staging investigations did not identify disease at any other site.

Epstein-Barr virus (EBV) has been associated with the development of salivary gland T cell NHL,^{1,2} but in this case in situ hybridisation for Epstein-Barr virus (EBV) encoded early nuclear RNA (EBER) was negative in the neoplastic cells. DNA extracted from paraffin wax embedded sections was submitted for polymerase chain reaction (PCR) analysis to detect clonal rearrangements of the immunoglobulin heavy chain (IgH) gene and of the T cell receptor γ (TCR γ) using the strategy described by McCarthy *et al.*² Clonal rearrangement of the IgH gene was not identified but reactions to detect rearrangement of the TCR γ gene disclosed a single monoclonal fragment (fig 2). The PCR products were cloned and the nucleotide sequence of seven independent clones was determined in both directions; five clones were found to have identical sequences. Comparison with the corresponding germ line sequences revealed that this consensus rearrangement was "out of frame" and therefore non-functional. This result provides indirect evidence that the neoplastic T cell population expresses TCR $\alpha\beta$ and not the TCR $\gamma\delta$.

Further staging investigations including clinical, haematological, and radiological examinations revealed no evidence of widespread disease.

The patient was treated initially with local radiotherapy to reduce the size of the parotid tumour, followed by systemic chemotherapy (CHOP regimen—cyclophosphamide, hydroxydaunorubicin (adriamycin), oncovin (vincristine), and prednisolone).

DISCUSSION

We report a case of primary T cell NHL of the parotid gland in an elderly white man, which was particularly notable for its close morphological resemblance to a low grade extranodal marginal zone NHL of salivary gland mucosa associated lymphoid tissue. Primary T cell NHL of the salivary glands is rare in Western populations, the present case being only the third such case described. NHL of the salivary glands is an uncommon form of malignancy, accounting for 5% of cases of extranodal lymphoma, and 10% of malignant diseases of the salivary glands.³ Most cases that are bone fide primary lesions of the salivary glands are B cell extranodal marginal zone NHL, usually arising on a background of myoepithelial sialadenitis. This case demonstrates that primary T cell lymphoma of

Abbreviations: ALK1, anaplastic lymphoma kinase antibody; CHOP regimen, cyclophosphamide, hydroxydaunorubicin (adriamycin), oncovin (vincristine), and prednisolone; EBER, Epstein-Barr virus encoded early nuclear RNA; EBV, Epstein-Barr virus; IgH, immunoglobulin heavy chain; MACOP regimen, methotrexate, adriamycin (doxorubicin), cyclophosphamide, oncovin (vincristine), and prednisolone; NHL, non-Hodgkin's lymphoma; NK, natural killer; PCR, polymerase chain reaction; TCR, T cell receptor; TdT, terminal deoxynucleotidyl transferase

Figure 1 (A) Salivary gland tissue diffusely infiltrated by neoplastic cells (haematoxylin and eosin, original magnification, $\times 65$). (B) At a higher magnification, foci of neoplastic cells are seen permeating ductal epithelium (arrow) in a manner reminiscent of lymphoepithelial lesions (haematoxylin and eosin, original magnification, $\times 265$). (C–E) Immunohistochemistry shows that the neoplastic cells stain positively for markers of T cell histogenesis (CD5 (C) and CD3 (D)), but are negative for B cell markers, a stain for CD20 (E) being representative.

Figure 2 A single clonal rearranged band is detected in the DNA from our patient (lane 3) and DNA from known cases of T cell non-Hodgkin's lymphoma acting as positive controls (lanes 1 and 2). A standard control tissue showed two rearranged bands (lane 5) and a polyclonal smear was seen from a reactive lymph node (lane 4). The omission of test DNA from the PCR reaction acted as a negative control (lane 6). Lane 7 shows DNA molecular size markers (Boehringer Mannheim, marker 5). An immunoglobulin heavy chain gene rearrangement was not identified.

the salivary gland can mimic closely a low grade extranodal marginal zone B cell lymphoma. However, the lack of evidence of pre-existing sialadenitis or evidence of underlying auto-

immune disease may prompt consideration of an alternative diagnosis, and recourse to immunohistochemistry and gene rearrangement studies should readily distinguish this lesion from primary B cell marginal zone lymphomas, which are more commonly encountered in the salivary glands. There was no evidence to suggest that the tumour in this case was nodally based, either arising in an intrasalivary lymph node or representing extensive nodal or extranodal disease secondarily involving the salivary gland.

"Primary T cell non-Hodgkin's lymphoma of the salivary glands is rare in Western populations, the present case being only the third such case described"

The histological features of cases described in the literature are variable (table 1). A review of the literature discloses that primary T cell lymphoma of the salivary glands is rare, with only 14 cases described, all but two of which have been from Oriental countries. The parotid and submandibular glands are the most frequently involved salivary tissues, although occasional cases are described in the sublingual glands. The most frequent histological type of this condition is a peripheral T cell lymphoma, often of low grade morphology, although occasionally pleomorphic. Staining for markers indicative of NK cell differentiation further identifies a few cases of angiocentric T/NK lymphomas and a similar number of cases of T anaplastic large cell lymphoma are also described. Of the 11 cases where data have been recorded, in seven cases

Table 1 Histological features of cases of primary T cell lymphoma of the salivary glands described in the literature (including our case)

Refs	Sex	Age	Ethnic origin	Family history	Site of disease	Histology	EBV status (ISH or IHC)	Treatment	Survival
4	M	46	Chinese	N/A	Submandibular	T-NHL	Negative	N/A	6 months
	M	65	Chinese	N/A	Parotid	T-NHL	Negative	N/A	36 months
	M	24	Chinese	N/A	Submandibular	T/NK angiocentric	Positive	N/A	6 weeks
	M	64	Chinese	N/A	Parotid	T/NK	Positive	N/A	5 months
	M	63	Chinese	N/A	Submandibular	T/NK angiocentric	Positive	Multimodality treatment not otherwise specified	>18 months
3	M	62	Chinese	N/A	Parotid	T anaplastic large cell	Negative	Multimodality treatment not otherwise specified	>48 months
	N/A	N/A	Chinese	N/A	Sublingual	T-NHL	Positive	N/A	N/A
	N/A	N/A	Chinese	N/A	Sublingual	T-NHL	Positive	N/A	N/A
	N/A	N/A	Chinese	N/A	Submandibular	T-NHL	Positive	N/A	N/A
5	M	48	N/A	N/A	Parotid	T anaplastic large cell	N/A	N/A	N/A
	M	71	N/A	N/A	Parotid	T anaplastic large cell	N/A	N/A	N/A
	N/A	N/A	N/A	N/A	N/A	T-NHL	N/A	N/A	N/A
6	M	79	N/A	N/A	Submandibular	T-NHL pleomorphic	Positive	Chemotherapy MACOP	N/A
7	N/A	N/A	N/A	N/A	N/A	Peripheral T cell	N/A	N/A	N/A
Our case	M	69	White	Nil	Parotid	T-NHL	Negative	See text	>30 months

EBV, Epstein-Barr virus; ICH, immunohistochemistry; ISH, in situ hybridisation; MACOB, methotrexate, adriamycin (doxorubicin), cyclophosphamide, oncovin (vincristine), and prednisolone; N/A, data not available/commented on in the original literature; NHL, non-Hodgkin's lymphoma; NK, natural killer cell.

Take home message

- T cell lymphoma in the salivary gland can closely mimic the morphological features of B cell extranodal marginal zone lymphoma

the tumour cells harboured EBV, with all of the previously reported T/NK lymphomas being positive for EBV. In our case, the failure to identify evidence of EBV infection is consistent with the immunohistochemical findings, which indicate a peripheral T cell (CD56 negative) rather than a T/NK cell phenotype.

Apart from EBV infection, which has been implicated in approximately 50% of cases of salivary T cell NHL, a background of autoimmune sialadenitis or enteropathy has been suggested as a predisposing factor to the development of this unusual form of extranodal lymphoma⁶; there was no clinical or laboratory evidence of either in our patient.

The case reported by James *et al* was treated by chemotherapy initially, using a low dose MACOP regimen (methotrexate, adriamycin (doxorubicin), cyclophosphamide, oncovin (vincristine), and prednisolone), followed by a full dose regimen because of the lack of response.⁶ The treatment regimen of the remaining cases were not detailed in the primary references except for two cases described by Chan *et al*,³ in which multimodality treatment had been given, but further details were not included in the paper.

Very few studies have alluded to the prognosis for this type of lymphoma. The experience of Chan *et al* suggests a variable outcome, with survival after diagnosis ranging from six weeks to more than four years.¹ The two patients who had the longest survival were EBV and CD56 negative, although one

apparently similar patient survived for only six months. To date, the patient described in our report remains disease free more than 30 months after diagnosis.

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