A case of coexisting Warthin tumor and langerhans cell histiocytosis associated with necrosis, eosinophilic abscesses and a granulomatous reaction in intraparotid lymph nodes

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Abstract

We present a patient (50-year-old male) with coexisting Warthin tumor and involvement of two intraparotid lymph nodes by Langerhans cell histiocytosis associated with necrosis, eosinophilic abscesses and a granulomatous reaction. This is the second documented case of this unusual combination of histological changes in nodal Langerhans cell histiocytosis and the first case involving intraparotid lymph nodes occurring together with an ipsilateral Warthin tumor.

Introduction

Langerhans cell histiocytosis (LCH) is a relatively rare proliferative histiocytic disorder of unknown cause affecting a subset of antigen presenting dendritic cells that is associated with lesional infiltration of eosinophilic granulocytes. Some authors believe that LCH is a neoplastic process, while other studies suggest that it may be of a polyclonal (reactive) nature. The Langerhans cells characteristically express CD1a, langerin and S100 protein with immunohistochemistry (IHC) and display a peculiar organelle, the Birbeck granule on ultrastructural examination. LCH most commonly affects children and there is a male predilection with a male:female ratio of 3-4:1. The most commonly affected organ is bone (uni- or multifocal involvement, the latter historically referred to as Hand Schüller Christian disease), followed by skin, lung and lymph nodes. Lymph node affliction is less common and is typical for the multisystemic form. Rarely, LCH may be disseminated with involvement of multiple visceral sites (Letter-Siwe disease). LCH very rarely affects the major salivary glands.[1,2] Necrosis together with a prominent granulomatous response associated with LCH featuring eosinophilic abscesses has been previously reported in one case report (cervical lymph node).[3] This event has, to the best of our knowledge, never been described in a major salivary gland. In this report, we present a patient where this occurred in parotid gland lymph nodes and where the parotid gland harboured a metachronous Warthin tumor.

Case Report

A 50-year-old smoking Chinese man with a history of a left Warthin tumor 5 years ago, presented with a painless right parotid swelling which had been increasing in size for 2 weeks duration and right inguinal lump for 1 week. On physical examination, there was a nodular, well circumscribed 2.5 cm right parotid mass. No facial nerve palsy was present. A full blood count pre-operatively showed leukocytosis (14.13×10^9/L; normal 4-11×10^9/L) with eosinophilia (2.68×10^9/L; normal 0.04-0.40×10^9/L). A fine needle aspiration (FNA) of the parotid lesion was performed and subsequently, a right superficial parotidectomy was performed. Ultrasonographic examination of the right inguinal lump indicated the presence of an enlarged lymph node (size 2 cm). Excision biopsy of the inguinal lymph node was performed on the same day as the parotidectomy. Four months after the operation, there was still mild leucocytosis (11.70×10^9/L) with eosinophilia (11.70×10^9/L). Erythrocyte sedimentation rate was within normal range (9 mm/hr). Computed tomography scans showed no evidence of multiorgan involvement.

Materials and Methods

The tissue was fixed in neutral formalin, embedded in paraffin, 4 µm thick sections were cut and stained with hematoxylin and eosin (H&E). An immunohistochemical study with commercial antibodies using protocols according to the manufacturers' recommendations was employed. Antibodies to the following antigens; CD1a, S100 protein and CD68, were employed. Special stains Ziehl Neelsen (ZN), Periodic-acid Schiff (PAS), Gomori Methenamine Silver (GMS) and Warthin-Starry (WS) were performed. Tissue from the inguinal lymph node was sent for flow cytometry analysis.

Results

The FNA showed sheets of oncocytic cells without atypia in a background of small lymphocytes, i.e. features of a Warthin tumor. No evidence of LCH or eosinophils were seen.

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On gross examination, the salivary gland showed a well circumscribed, unencapsulated, light brown mass measuring 2.4 cm in maximum dimension. Apart from the above mentioned nodular mass, two enlarged nodular (the largest 1.5 cm) intraparotid lesions were identified. The rest of the parotid gland parenchyma was unremarkable. Histological examination of the 2.4 cm parotid nodule confirmed the FNA diagnosis of a Warthin tumor (Figure 1A). In addition, four intraparotid lymph nodes were detected, two of which corresponded to the nodular lesions identified grossly. The two enlarged lymph nodes were almost entirely replaced by sheets of eosinophilic granulocytes, irregular areas of necrotic material among sheets and scattered nests of mononuclear cells with moderately abundant cytoplasm and convoluted nuclei featuring distinct nuclear grooves. (Figure 2A-D). In several areas, sheets and aggregates of mononuclear histiocytic cells which did not

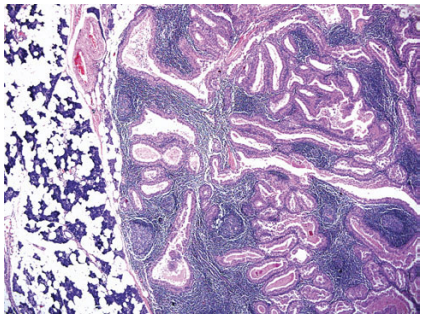

Figure 1. Hematoxylin and eosin stained section of the Warthin tumor with classic histological features.

display the nuclear grooves and which focally contained abundant intracellular Charcot-Leyden crystals were seen (Figure 3A,B). Scattered mitotic figures were detected, but no atypical forms were seen. There was no evidence of reaction (haemorrhage, hemosiderin depositions and/or granulation tissue) to the previous FNA procedure in the lymph nodes. No evidence of vasculitis, Reed-Sternberg-/Hodgkin- or other atypical lymphoid cells including polykaryocytes were identified. Special stains (PAS, GMS, ZN and WS) did not reveal any infective organisms. Non-lesional salivary gland parenchyma was histologically unremarkable.

The immunohistochemical study showed that the sheets of histiocytic cells (without nuclear grooves), frequently rimming the basophilic necrotic material with eosinophilic abscesses were distinctly positive for CD68 and negative for CD1a and S100 protein (Figure 3C). Conversely, the mononuclear cells with convoluted, grooved nuclei displayed strong immunoreactivity for CD1a and S100 protein and were negative for CD68 (Figure 3D,E).

The results from the flow cytometry analysis gave no evidence of lymphoproliferative disease. A diagnosis of Warthin tumor with associated lymph node involvement by Langerhans cell histiocytosis with necrosis, eosinophilic abscesses and a granulomatous reaction was made. Routinely stained sections and IHC of the right inguinal lump confirmed a lymph node involved by Langerhans cell histiocytosis and eosinophilic abscesses, but no necrosis or granulomatous component were present.

Discussion

We herein report an unusual case of LCH occurring together with eosinophilic abscesses, necrosis and a granulomatous tissue response in intraparotid lymph nodes where the salivary gland harboured a metachronous Warthin tumor. LCH is a proliferative histiocytic disorder of unknown cause affecting the bone marrow derived antigen presenting Langerhans cell, which most commonly occur in children, but may affect patients of a wide age range. Most frequently the skeleton is affected, but a wide range of organs such as skin, lungs, lymph nodes, thyroid, pituitary, thymus, orbit, gastrointestinal tract and central nervous system may be affected.[4-9] LCH affecting intra parotid lymph nodes is a rare phenomenon.[1,2] LCH occurring together with a granulomatous reaction and eosinophilic abscesses has, to the best of our knowledge, only been documented in one previous case report.[3] This patient was a 30-year-old man who presented with left cervical lym-

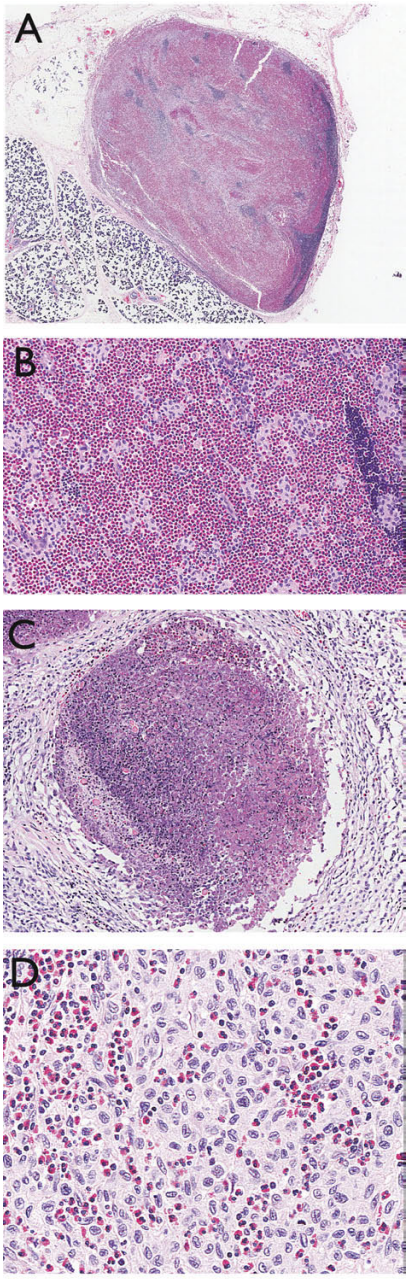

Figure 2. Low power (hematoxylin and eosin) showing one of the intraparotid lymph node almost totally replaced by sheets of eosinophilic and pale areas (A). The eosinophilic areas were composed of sheets of eosinophilic granulocytes (eosinophilic abscesses) with interspersed small aggregates of pale mononuclear cells (B). Scattered foci with necrosis were present within the lymph nodes (C). The pale mononuclear cells were seen arranged in sheets. The nuclei were convoluted and displayed grooves (D).

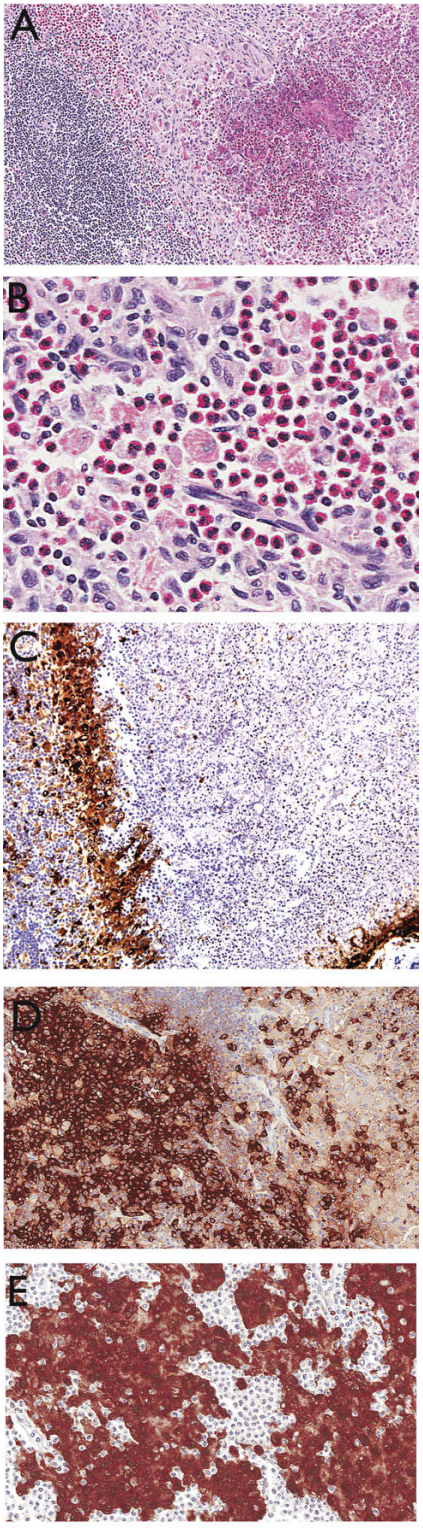

Figure 3. Epithelioid histiocytes were seen rimming areas of necrosis (A). These cells frequently contained prominent intracellular Charcot-Leyden crystals (B). The histiocytic cells rimming the necrotic areas were distinctly positive for CD68 (C). Langerhans cells demonstrate strong immunoreactivity for CD1a (D; note negative mononuclear histiocytic cells to the right) and S100-protein (E).

phadenopathy of 2 months duration. No associated salivary gland pathology was reported in this patient.

The finding of a lymph node in the head and neck region with eosinophilic abscesses accompanied by necrosis and a granulomatous lymphadenitis vouches for a few differential diagnostic possibilities. Necrosis associated with an infiltrate composed of neoplastic cells with immunohistochemical features (positivity for CD1a and S100 protein) of Langerhans cells is significantly more frequently seen in Langerhans cell sarcoma (LCS) than LCH. However, the cytomorphological features in LCS are overtly malignant with nuclear pleomorphism and prominent nucleoli, which were absent in the case presented herein. Churg-Strauss syndrome (CSS) with involvement of lymph nodes is characterized by infiltration of eosinophils associated with necrotizing and/or non-necrotizing granulomas, vasculitis and lymphoid follicular hyperplasia. Cases of CSS involving the parotid gland and lymph nodes are on record, both in the setting of widespread systemic disease, but also as manifestation of a limited form of disease.[10,11]

Although our patient had blood eosinophilia, the absence of vasculitic changes and the presence of highly characteristic Langerhans cells mitigate against this differential diagnostic alternative. A serologic analysis for antineutrophil cytoplasmic antibody (p-ANCA) would be helpful in regard to CSS (not done in our patient). In addition, no case of CSS in association with LCH has been reported to date. LCH may rarely be associated with peripheral eosinophilia. The case presented by Tan *et al.*[3] also showed peripheral eosinophilia in addition to the abundance of eosinophils in the affected lymph node with the formation of eosinophilic abscesses. Interestingly, Ohnishi et al have reported one patient (25 year old male) with multifocal osseous involvement by LCH and blood eosinophilia who developed chronic eosinophilic leukemia with a FIP1L1-PDGFRA gene fusion and T674I mutation after chemotherapy. These genetic aberrations were not identified in the pre-chemotherapy specimens.[12]

Sheets of histiocytic-type cells in a lymph node in the head and neck region, would also raise the possibility of Rosai-Dorfman disease (RDD)/sinus histiocytosis with massive lymphadenopathy. RDD has been reported to occur concurrently with LCH.[13] However, the cytomorphological features of the lesional cells in RDD differ from LCH. The large histiocytic cells of RDD have round to oval nuclei with no significant folding or grooves and more abundant cytoplasm. A variable phagocytosis of lymphocytes (emperipolesis) is always present (not seen in our case). Although the cells of RDD are positive for S100 protein, the cells are consistently negative for CD1a on IHC.

Kimura's disease (KD) associated with a granulomatous reaction has been reported previously.[14] However, we did not find any polykaryocytes and the characteristic extensive fibrosis seen in KD was not present. Moreover, no extranodal extension with involvement of the perinodal soft tissue or lymphoid follicular hyperplasia as characteristically seen in KD was present. Again, the presence of lesional cells with the characteristic light microscopic features and immunohistochemical properties of LCH strongly argue against KD. Furthermore, KD has not been reported to be associated with LCH.

Various lymphomas, including Hodgkin lymphoma may be associated with a significant number of Langerhans cells.[15-17] Reportedly, rare cases of, Langerhans cell histiocytosis in the parotid glands have shown light microscopical features resembling marginal zone lymphoma.[1] In our case, no atypical cells with features of Reed Sternberg cells including variant forms were detected. In addition, the results of the flow cytometry analysis (from the inguinal lymph node) did not support the possibility of a lymphomatous process. Interestingly, a rare case of anaplastic large cell lymphoma with light microscopical features mimicking LCH is on record,[18] but again no atypical lymphoid cells (including hallmark cells) were seen in our case.

Dendritic cell sarcomas e.g. interdigitating dentritic cell- (IDRCS) and follicular dendritic cell sarcomas (FDCS) are rare tumours arising from dendritic cells in lymphoid tissue. Histologically, the tumor cells in IDRCS and FDCS may appear epithelioid (although more frequently spindly) and frequently display bland nuclear features with occasional grooving. Lesional cells are intermingled with lymphocytes and plasma cells (but not eosinophils) and are arranged in fascicles and/or sheets (less frequently in a storiform pattern). Although S100 protein is frequently detectable by IHC in these neoplasms, CD1a is most frequently negative, although two cases of IDRCS with positive immunereactivity for CD1a are on record.[19-21]

Another differential diagnostic consideration in a lymph node with sheets of histiocytic-type cells, would be nodal involvement by juvenile xanthogranuloma (JXG) in the setting of systemic disease. This disease most frequently occurs in the pediatric population, but one adult case with parotid involvement of juvenile xanthogranuloma has been reported.[22] JXG is frequently associated with a mixed inflammatory infiltrate that may contain a significant number of eosinophils and in early stages of the disease, lesional cells may display an absence of lipidized cytoplasm. Notably, multinucleated Touton giant cells are less prevalent at non-dermal sites. The nuclear features are bland with no significant convolution and/or grooves as seen in LCH. Moreover, although S100 protein positivity is seen in a minority of cases (20%), CD1a is consistently negative. Similarly, nodal involvement by reticulohistiocytoma, also as a manifestation of widespread disease (reticulohistiocytosis), with multifocal involvement of skin and mucous membranes in conjunction with severe arthropathy, display lesional cells with abundant homogenous to finely granular cytoplasm with a ground glass appearance. A variable component of multinucleated cells is frequently seen (especially in older lesions). The nuclear morphology is different from LCH (absence of convolution and grooves) and the cells are positive for CD68 and with rare exceptions negative for S100 protein and CD1a on IHC.

Other causes which might incite a granulomatous inflammation are mycobacterial, fungal or parasitic infections. Granulomas with central necrosis surrounded by a mixed inflammatory infiltrate with numerous eosinophils and variable numbers of neutrophils, lymphocytes, and a palisade of epithelioid histiocytes and/or giant cells with Charcot-Leyden crystals has been recognized as a characteristic lesion with relationship to visceral larva migrans.[23] However, to the best of our knowledge, the occurrence of such lesions have never been reported in lymph nodes. In addition, most patients in the reported cases had remnant parasites identified within the affected tissue. No such parasitic structures were seen in our case.

Awareness of the fact that LCH may be associated with a necrotizing granulomatous tissue response occurring in conjunction with eosinophilic abscesses should aid in making the correct diagnosis. If in doubt, performing a limited immunohistochemical study with CD1a, S100 protein and CD68 would facilitate the identification of the two different cellular (histiocytic; reactive and Langerhans cell; neoplastic) components.

In conclusion, we present a patient with intraparotid lymph node involvement by Langerhans cell histiocytosis featuring the unusual combination of necrosis, eosinophilic abscesses and a granulomatous reaction. The association with a metachronous Warthin tumor is most likely coincidental.

References

1. Kojima M, Itoh H, Shimizu K, et al. Incidental Langerhans cell histiocytosis of the parotid gland resembling marginal zone B-cell lymphoma: a case report. J Oral Pathol Med 2006;35:630-2.
2. Darvishian F, Hirawat S, Teichberg S, et al. Langerhans' cell histiocytosis in the parotid gland. Ann Clin Lab Sci 2002;32: 201-6.

3. Tan HW, Chuah KL, Goh SG, et al. An unusual cause of granulomatous inflammation: eosinophilic abscess in Langerhans cell histiocytosis. J Clin Pathol 2006;59:548-9.
4. Garofalo D, Cutfield R. Pituitary involvement in Langerhans-cell histiocytosis. N Z Med J 2010;123:88-91.
5. Priyambada L, Bhatia V, Krishnani N, et al. Primary Hypothyroidism, Precocious Puberty and Hypothalamic Obesity in Langerhans Cell Histiocytosis. Indian J Pediatr.
6. Hernandez Perez JM, Franquet Casas T, Rodriguez S, Gimenez A. [The Langerhans cell histiocytosis with thymic localization as initial and exclusive place]. An Med Interna 2007;24:497-9.
7. Das JK, Soibam R, Tiwary BK, et al. Orbital manifestations of Langerhans Cell Histiocytosis: A report of three cases. Oman J Ophthalmol 2009;2:137-40.
8. Shima H, Takahashi T, Shimada H. Protein-losing enteropathy caused by gastrointestinal tract-involved Langerhans cell histiocytosis. Pediatrics 2010;125: e426-32.
9. Grois N, Fahrner B, Arceci RJ, et al. Central nervous system disease in Langerhans cell histiocytosis. J Pediatr 2010;156:873-81.
10. Casey M, Radel E, Ratech H. Lymph node manifestations of limited Churg-Strauss syndrome. J Pediatr Hematol Oncol 2000;22:468-71.
11. Gambari PF, Ostuni PA, Lazzarin P, et al. Eosinophilic granuloma and necrotizing vasculitis (Churg-Strauss syndrome?) involving a parotid gland, lymph nodes, liver and spleen. Scand J Rheumatol 1989;18:171-5.
12. Ohnishi H, Kandabashi K, Maeda Y, et al. Chronic eosinophilic leukaemia with FIP1L1-PDGFRA fusion and T6741 mutation that evolved from Langerhans cell histiocytosis with eosinophilia after chemotherapy. Br J Haematol 2006;134: 547-9.
13. O'Malley DP, Duong A, Barry TS, et al. Co-occurrence of Langerhans cell histiocytosis and Rosai-Dorfman disease: possible relationship of two histiocytic disorders in rare cases. Mod Pathol 2010;23:1616-23.
14. Hosaka N, Minato T, Yoshida S, et al. Kimura's disease with unusual eosinophilic epithelioid granulomatous reaction: a finding possibly related to eosinophil apoptosis. Hum Pathol 2002;33: 561-4.
15. Benharroch D, Guterman G, Levy I, Shaco-Levy R. High content of Langerhans cells in malignant lymphoma - incidence and significance. Virchows Arch 2010;457:63-7.
16. Naumann R, Beuthien-Baumann B, Fischer R, et al. Simultaneous occurrence of Hodgkin's lymphoma and eosinophilic granuloma: a potential pitfall in positron emission tomography imaging. Clin Lymphoma 2002;3:121-4.
17. Christie LJ, Evans AT, Bray SE, et al. Lesions resembling Langerhans cell histiocytosis in association with other lymphoproliferative disorders: a reactive or neoplastic phenomenon? Hum Pathol 2006;37:32-9.
18. Ezra N, Van Dyke GS, Binder SW. CD30 positive anaplastic large-cell lymphoma mimicking Langerhans cell histiocytosis. J Cutan Pathol 2010;37:787-92.
19. Gan MF, Lu HS, Zhang JW, Yu XR. [Interdigitating dendritic cell sarcoma/tumor: a study of 3 cases]. Zhonghua Bing Li Xue Za Zhi 2008;37:676-9.
20. Yin WH, Yu GY, Ma Y, et al. [Follicular dendritic cell sarcoma: a clinicopathologic analysis of ten cases.]. Zhonghua Bing Li Xue Za Zhi 2010;39:522-7.
21. Orii T, Takeda H, Kawata S, et al. Differential immunophenotypic analysis of dendritic cell tumours. J Clin Pathol 2010;63:497-503.
22. Dhouib H, Hammami B, Sellami M, et al. [Xanthogranuloma of the parotid gland in adults]. Rev Stomatol Chir Maxillofac 2010;111:337-9.
23. Kaplan KJ, Goodman ZD, Ishak KG. Eosinophilic granuloma of the liver: a characteristic lesion with relationship to visceral larva migrans. Am J Surg Pathol 2001;25:1316-21.