Extranodal NK/T-cell Lymphoma with Angiocentric Pattern presenting as Lethal Midline Granuloma

Khaleeq-Ur-Rehman¹, Clive E Moss², Andrew MS Brown³, E Lynn Jones⁴ and John Hamburger⁵

¹ Medical student, University of Birmingham, England.
² Specialist Registrar, Oral & Maxillofacial Surgery, University Hospital Birmingham, England.
³ Consultant, Oral & Maxillofacial Surgery, University Hospital Birmingham, England.
⁴ Professor of Pathology, Department of Pathology, Birmingham Medical School, England.
⁵ Consultant, Oral Medicine, Birmingham Dental Hospital, England.


A case of malignant midline oral ulceration in a 51-yr-old woman is reported. Midline granuloma is rare, well documented and has a variety of names. Lethal midline granuloma is a malignant lymphoma, most commonly NK or T cell lineage. The patient developed recurrent oral ulceration over a period of a year requiring several biopsies before the correct diagnosis was made. A high grade NK/T cell lymphoma with an angiocentric growth pattern was confirmed, the lymphoma cells expressing T-cell markers (CD3, CD43) and co-expressing CD30. Natural killer T-cell markers (CD56 and CD57) were not expressed but there are strong expression cytotoxin granule associated proteins granzyme B and perforin markers of activated NK cells. No association with Epstein-Barr virus was found with immunohistochemistry and in-situ hybridisation. The patient failed to respond to chemotherapy and died several months later. This case illustrates the difficulty in making the diagnosis of T-cell lymphoma as the oral ulcers often show secondary inflammatory changes, which mask the lymphoma cells, and multiple biopsies may be required to make the correct diagnosis.

Key words: NK/T Cell Lymphoma, Angiocentric, Lethal Midline Granuloma

Correspondences: Khaleeq-Ur-Rehman, 15 Chapel Street Lye Stourbridge West Midlands England DY9 8BT Phone: 01-384-423992, E-mail: rehman_ku@hotmail.com

Introduction

Midline destruction presenting in the mouth is rare but well documented. Lethal or malignant midline granuloma (LMG) has been given many other names and descriptions (1). McBride (1897) was one of the first to bring the condition to light with his pictures of a case of midline destruction (2), while in 1939 Stewart described midline lesions that were characterized by a polymorphous inflammatory infiltrate (3). Wegener, (4) also in 1939, described a necrotising granulomatous process of the midface accompanied by systemic complications involving the kidneys and the lungs, which was found to be less destructive than LMG. Eichel (5) in 1966 used the term polymorphic reticulosis that was found to be histologically similar to Stewart’s granuloma. Malignant midline reticulosis was the term used by Kassel 1969 (6), and Liebow (7) in 1972 used the name lymphomatoid granulomatosis. Histological similarities existed between all these conditions Jaffe (8-9) in the mid eighties used the term angiocentric immunoproliferative lesions (AIL) to describe them all.

We present a case of malignant ulceration involving the midline hard and soft palate, hypopharynx and posterior third of the tongue caused by a high-grade NK/T-cell lymphoma.

Case report

A 51-year-old Caucasian female patient presented with severe oral ulceration, difficulty in eating and progressive weight loss. She was initially seen by a gastroenterologist in August 1999, who made a diagnosis of oral candidosis. She was prescribed Nystatin with little benefit. A barium meal and endoscopy and routine blood investigations performed to eliminate any gastrointestinal causes, proved normal. Autoimmune antibody screen, including antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA) and anti-epidermal antibodies was negative.
Initial biopsy of the palatal lesion on 20/8/99 revealed non-specific chronic inflammatory cell changes. She was started on Prednisolone 40mg daily with some improvement, but at the six-week review appointment, the oral ulceration had got worse. She was admitted and a second biopsy on 21/9/99 from the same site revealed the appearances of aphthous ulceration with a mixed inflammatory cell reaction in the oral mucosa and submucosa with extension into minor salivary gland tissue. Immunohistological staining showed a mixed population of T and B-lymphocytes. Routine blood investigations including Vit. B12, folate and anti-endomysial antibodies were again all negative. Barium meal and follow through and colonoscopy demonstrated no abnormality. She continued to take Prednisolone with little effect and the addition of Thalidomide also failed to resolve her symptoms. She was referred to Birmingham Dental Hospital for further management. On presentation her mouth ulceration was complicated by supervening anaerobic infection that was treated with a course of Metronidazole.

Thalidomide was replaced by Azathioprine with some improvement, but more aggressive ulceration involving the palate and hypopharynx having the appearance of necrotising stomatitis soon developed. The blood
results reported marked lymphopenia of 0.3x10^9/l and this was believed to be due to Azathioprine, which was discontinued.

The early suspicion of Wegener’s granulomatosis was considered to be unlikely with two negative ANCA results and an erythrocyte sedimentation rate (ESR) of less than 2mm/h and no evidence of vasculitis on mucosal biopsies. The patient was then sent to Selly Oak Hospital as a matter of urgency because she was having difficulty eating and presented with signs of dehydration. On presentation in the clinic she had large areas of erosions involving the hard and soft palate, uvula, posterior wall of pharynx and posterior third of the tongue (Figs. 1, 2). She was admitted and fed via a nasogastric tube.

Pain relief was achieved with opioid analgesics (MST 60mg bd) and regular Tetracycline and Mucain mouthwashes. Incisional biopsies of the palatal and pharyngeal lesions carried out on 9/11/99 under general anaesthetic showed ulceration, and a mixed acute and chronic inflammatory cell reaction but no definite evidence of lymphoma. A second series of biopsies a few weeks later from the same areas showed ulceration, inflammatory exudate, necrotic granulation tissue and a moderately dense mixed inflammatory cell reaction in the submucosa. Areas of necrosis were seen and in addition there was a population of intermediate-size lymphoid cells with round basophilic nuclei and occasional large lymphoid blast cells. Immunohistological staining was done by the streptavidin-biotin peroxidase complex (SABC) technique with the Dako Strept ABC complex/HRP Duet mouse/rabbit kit (Dako, Denmark) following antigen retrieval by microwaving. The sources and concentrations of the antibodies used are listed in table 1. Immunostaining revealed a T-phenotype with CD3 positivity (Fig. 3) but negative staining for CD30. The appearances were suggestive of a high-grade NK/T-cell lymphoma. Bone marrow trephine biopsy proved negative initially for lymphoma and samples sent to the regional genetic laboratory were tested for lymphoma. Out of the 26 cells examined 22 were of normal female karyotype but 4 cells had abnormal karyotype of 46 chromosomes with deletion of most of the long arm of one chromosome 9. These results were
consistent with the diagnosis of lymphoma. T-cell receptor gene rearrangement studies were not performed. Staging computed tomography (CT) scans of the chest and abdomens were all normal although cervical lymphadenopathy noted.

Daily nutritional requirements were initially achieved by nasogastric and oral feeding, but later necessitating a percutaneous gastrostomy. The patient was discharged from the ward a week later pain free and managing sufficient oral intake.

The treatment plan, consisting of six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy followed by radiotherapy was developed.

The patient started chemotherapy and after each cycle she was admitted for neutropenic sepsis requiring intravenous (iv) antibiotics. Peritonsillar arterial bleeding necessitated surgical intervention for the arrest of hemorrhage. Three cycles of chemotherapy did little to improve her condition, leading to doubts about the correct diagnosis. A further biopsy of an ulcer on the posterior third of the tongue showed a mixed acute and chronic inflammatory cell exudate associated with necrosis and an infiltrate of intermediate-to-large atypical lymphoid blast cells with vesicular polylobated nuclei. These cells were centered around and invading small blood vessels (Figs. 4, 5) showing an angiocentric and angioinvasive pattern. Immunohistological staining showed a T-phenotype with the larger lymphoid cells expressing CD3, CD30 and CD43. The larger cells showed strong cytoplasmic expression of the cytotoxic granule associated proteins granzyme B (Fig. 6) and perforin. They were negative for CD4, CD5, CD8, CD10, CD15, CD20, CD34, NK/T-cell markers CD56 and CD57 but there was strong expression of CD3, CD30, CD43, granzyme B and perforin but the cells were negative for CD4, CD5, CD8, CD34 and the NK cell markers CD56 and CD57. There is wide geographical variation of nasal T/NK cell lymphomas. Lesions of this phenotype are uncommon in the western world but very common in the Far East and Latin America (14-15). The higher incidence of these cases in the East is mainly due to the fact that large proportions of these lymphomas have been linked with Epstein Barr Virus (EBV) and these infections are common in the East (16). A literature review by Lee et al (17) demonstrated EBV-DNA in 16 out of 21 reported cases. No association with EBV was found in this case.

Management of non-healing midline granuloma depends on appropriate evaluation of the patient. All relevant investigations need to be carried out to rule out any infectious causes such as tuberculosis, syphilis, deep fungal infection and squamous cell carcinoma. The lesions need to be biopsied in multiple sites with deep samples. The case reported here required several biopsies to establish a diagnosis due to the widespread necrotic nature of the lesion and the increased susceptibility to supervening infection making it difficult to obtain an adequate specimen. It is for this reason that biopsies are often reported as showing the appearances of acute and chronic inflammation.

Once a diagnosis of T-cell lymphoma has been made, several treatment modalities are available: antibiotics for infection, immunosuppressive drugs, radiation alone or with chemotherapy or chemotherapy alone (18). If all treatment fails, surgical removal with reconstruction is an option (19). The treatment chosen for our case was primary chemotherapy followed by radiotherapy.

Discussion

Sinonasal lymphomas are relatively uncommon. A more recent workshop in Hong Kong sponsored by the University of Hong Kong and the Society of Haematopathologist concluded that nasal T/NK cell lymphomas are a distinct clinicopathological entity. (10-11). They commonly feature as midline facial destructive lesions, often involving the palate and upper digestive tract and have several frequently-associated histological features such as angioinvasion, coagulative necrosis and epitheliotropism (12). Angiocentric tumors are defined as those where the cells are preferentially concentrated around or within blood vessels, with infiltration and destruction of the blood vessel walls.

Immunohistochemical techniques have shown that many T/NK cell lymphomas have peripheral T-cell phenotype, expressing T-cell markers such as CD2, CD3 and CD5. The NK cell phenotype is found in majority of these cases. The cells are positive for T-cell antigens such as CD2, CD43 and CD45 but lack CD3, CD4 and CD5. All these tumors usually possess the NK cell marker CD56 (12-13). This case presented showed a T-phenotype expressing CD3, CD30, CD43, granzyme B and perforin but the cells were negative for CD4, CD5, CD8, CD34 and the NK cell markers CD56 and CD57. There is wide geographical variation of nasal T/NK cell lymphomas. Lesions of this phenotype are uncommon in the western world but very common in the Far East and Latin America (14-15). The higher incidence of these cases in the East is mainly due to the fact that large proportions of these lymphomas have been linked with Epstein Barr Virus (EBV) and these infections are common in the East (16). A literature review by Lee et al (17) demonstrated EBV-DNA in 16 out of 21 reported cases. No association with EBV was found in this case.

Management of non-healing midline granuloma depends on appropriate evaluation of the patient. All relevant investigations need to be carried out to rule out any infectious causes such as tuberculosis, syphilis, deep fungal infection and squamous cell carcinoma. The lesions need to be biopsied in multiple sites with deep samples. The case reported here required several biopsies to establish a diagnosis due to the widespread necrotic nature of the lesion and the increased susceptibility to supervening infection making it difficult to obtain an adequate specimen. It is for this reason that biopsies are often reported as showing the appearances of acute and chronic inflammation.

Once a diagnosis of T-cell lymphoma has been made, several treatment modalities are available: antibiotics for infection, immunosuppressive drugs, radiation alone or with chemotherapy or chemotherapy alone (18). If all treatment fails, surgical removal with reconstruction is an option (19). The treatment chosen for our case was primary chemotherapy followed by radiotherapy.

References


4. Wegener FRG. Uber eine eigenartige rhinogene granulomatose unit besonden beteiligung des arteriensystemsder nieren. *Biets Pathol* 1939; **102**: 36. (German)


(accepted for publication September 19, 2003)