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Clinical Records

Non-Hodgkin's lymphoma of the external auditory canal in an HIV-positive patient

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Abstract
This is a case report of non-Hodgkin's lymphoma of the external auditory canal, and infratemporal fossa, which presented with multiple cranial nerve palsies. The diagnosis was achieved via biopsy of tissue from the external auditory canal, and treatment with radiation therapy led to improvement of the symptoms. The management of AIDS-related lymphoma of the skull base with cranial neuropathies is reviewed.

Key words: Lymphoma, non-Hodgkin's; Ear canal; Cranial nerve diseases; HIV seropositivity

Case report

A 36-year-old Hispanic female was diagnosed HIV-positive in 1991. Two years later she presented to her GP with night sweats and right ear pain. The diagnosis of acute otitis media was made and the patient was placed on amoxicillin/clavulanic acid (500 mg p.o. T.I.D.). There was no improvement after one week, so the medication was changed to oral ciprofloxacin and antibacterial otic drops. Two weeks later the patient developed vesicular lesions in her right external auditory canal and she was given acyclovoir for presumed Ramsey Hunt syndrome.

Despite the therapy, the ear pain progressed and a right facial paralysis developed. A few weeks later the patient presented to the emergency department and reported having had progressive difficulty with closing the right eye. She experienced moderate imbalance, but denied tinnitus, nausea, vomiting, or true vertigo. There was no cough or fever.

The physical examination revealed the cranial nerves II, III, IV, VI, IX, and XI to be intact. The right facial nerve had a paresis (House/Brackman Grade V/VI). The right second and third divisions of the trigeminal nerve demonstrated decreased sensation. The right hypoglossal nerve showed minimum decreased function. The left tympanic membrane was normal, but the right external auditory canal was filled with granulation tissue. The Weber tuning fork test lateralized to the right side and the Rinne tuning fork test reversed on the right side. Flexible nasopharyngoscopy revealed enlarged symmetric adenoids, patent eustachian tube orifices, normal laryngeal function and appearance. The presumptive diagnosis was malignant otitis externa.

The external ear granulation tissue was biopsied. Subsequent work-up included an audiogram which showed a maximum conductive hearing loss on the right, a CT scan which showed tissue or fluid within the mastoid air cells with preservation of the septa (Figure 1) and a technetium scan that showed increased activity in the mastoid area.

The initial biopsy was suggestive of a lymphoma and a repeat biopsy was definitive. The histopathology showed atypical lymphocytes with large cell immunoblastic phenotype plasmacytoid features (Figure 2). The L26 marker was positive for B-cells. The diagnosis of a high grade B-cell non-Hodgkin's lymphoma was made.

Further work-up included a magnetic resonance image (MRI) scan (Figure 3). This revealed a lobulated mass occupying the right infratemporal fossa. The tumour evidently grew up through the eustachian tube to present in the external auditory canal. A lumbar puncture was negative for malignant cells, but showed increased cellularity with lymphocytes and monocytes. One intrathecal dose of methotrexate was given at that time.

Radiotherapy was instituted to the nasopharynx and skull base (46 Gy were given in 23 single fractions over 37 days). The patient's disease responded well to treatment and the pain resolved three days after beginning the treatment. At completion of the therapy complete eye closure was possible and a remnant of the tympanic membrane remained. The patient's hearing improved and a repeat MRI scan showed the infratemporal fossa to be tumour-free.

The patient has since died from an opportunistic infection.

Discussion

Even before AIDS, non-Hodgkin's lymphoma (NHL) has been a growing problem. The incidence of NHL in both men and women in the USA and in other countries has been increasing over the last 20 years, and is still largely unexplained. In the USA there has been roughly a 50 per cent increase in incidence and a 22 per cent increase in the death rate since the early 1970s. In AIDS patients

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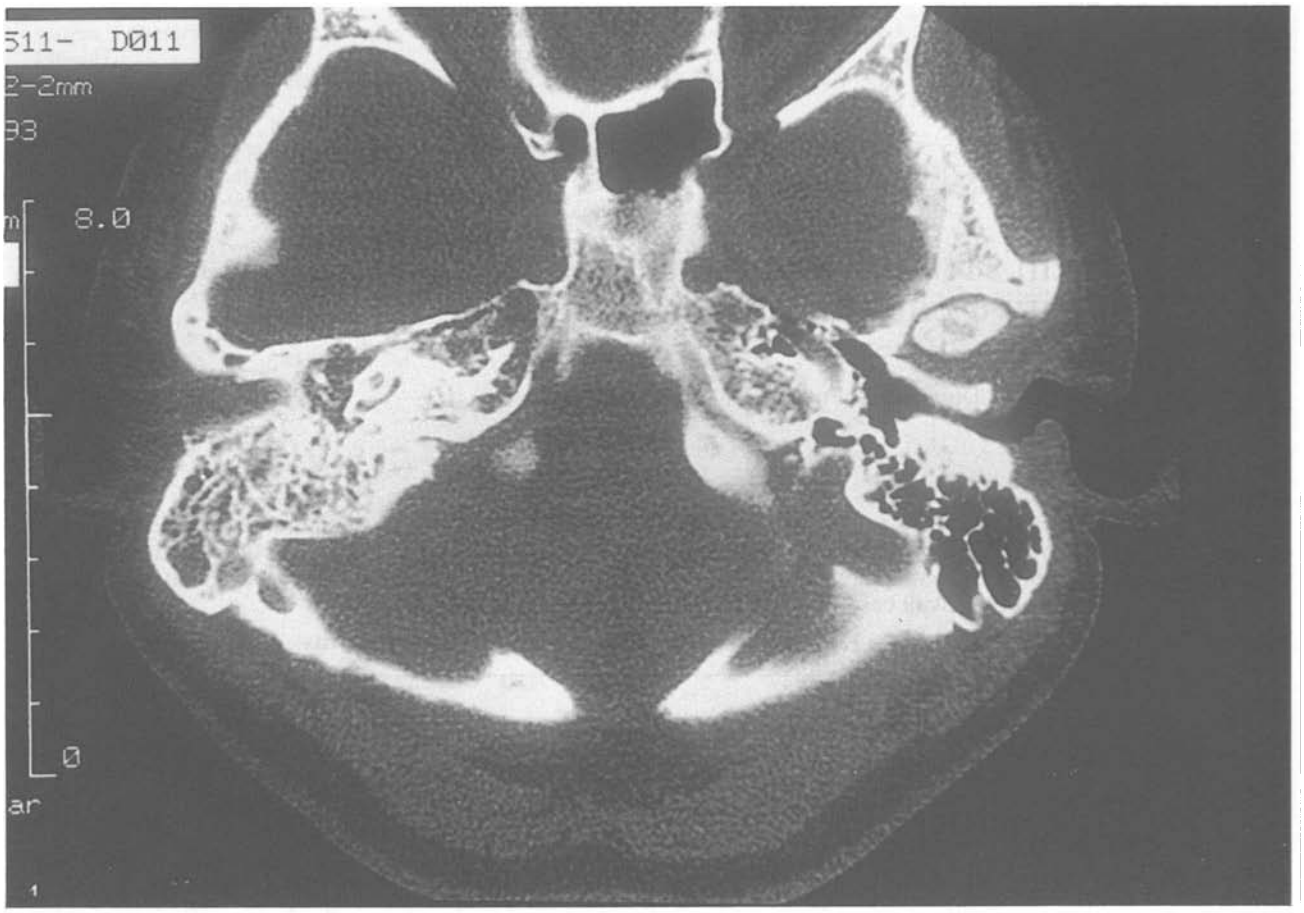

FIG. 1

CT scan showing tissue or fluid within the right mastoid air cells with preservation of the septa.

there is a 60–100-fold increase relative to that in the general population (Karp and Broder, 1991).

The immune system responds inappropriately in the HIV seropositive patient. The stimuli responsible for B-cell proliferation are numerous and include increased production of interlukin (IL) (IL1, IL2, IL4, IL6, IL7, IL10), interferon gamma, tumour necrosis factor, lymphotoxin, B-cell growth factor (25 and 50 kDa). Elevated serum levels of IL6 have been associated with the development of lymphoma and IL6 production is stimulated by HIV (Levine, 1992). HIV infection induces a cascade of cytokines or growth factors that serve to increase the replication of HIV and to induce B-cell growth. The responding gamma globulinopathy results in lymphoid tissue proliferation, often presenting as adenopathy, or as in this case lymphoma development (Zurlo, 1992).

Normal B-cell differentiation is accomplished through rearrangements of gene sequences that encode antigen receptors or immunoglobulins (Karp and Broder, 1991). Recombinase enzymes mediate DNA breakage and rejoining to create new immunoglobulins. These changes take place in the pre-B- and immature B-cells. Three gene sequences need to be arranged in a specific pattern V_H–D–J_H (variable–diversity–joining). The sequence is orderly but there is much variability within each segment. In addition all immunoglobulin gene regions have enhancer sequences that activate transcription over the whole chromosome.

Malignancies are characterized by preserved self-renewal capacity, but an inability for terminal differentiation. One pathway to malignancy is the translocation of a normal growth promoting gene into the specific antigen receptor gene or the so-called protooncogene. The enhancer sequence which is already present may activate the translocated growth-promoting gene and a functioning oncogene is created. Recent molecular studies implicate the translocation of bc1–1, bc1–2, and c-myc genes in lymphomagenesis.

The presence of the Epstein-Barr virus (EBV) and the development of B-lymphoproliferative diseases has been well recognized for three decades (Saemundsen *et al.*, 1981). In the AIDS patient impaired immune system surveillance from the CD4 cell confers a permissive effect on the expansion of multiple EBV-immortalized neoplastic B-cells clones (Levine, 1992). Cells from approximately 50 per cent of AIDS-related NHL contain EBV DNA sequences. In addition when EBV DNA and EBV nuclear antigen are detected in nodes from HIV-positive patients with generalized lymphadenopathy, their presence signifies the future emergence of non-Hodgkin's lymphoma.

Non-Hodgkin's lymphoma (NHL) is the second most common AIDS associated malignancy, after Kaposi's sarcoma. It is estimated that up to 30 per cent of HIV-positive patients will eventually acquire this disease. The incubation period between infection and the development of lymphoma is approximately 50 months which is similar to the incubation period for other opportunistic infections, and this is considered an AIDS defining illness (Saemundsen *et al.*, 1981). The risk for developing NHL is not uniform, but appears to increase at about two years after antiviral therapy with Zidovudine for full-blown AIDS (Karp and Broder, 1991). The estimated actuarial probability rises to 30 per cent after three years of retroviral therapy.

The majority of HIV-positive patients who develop

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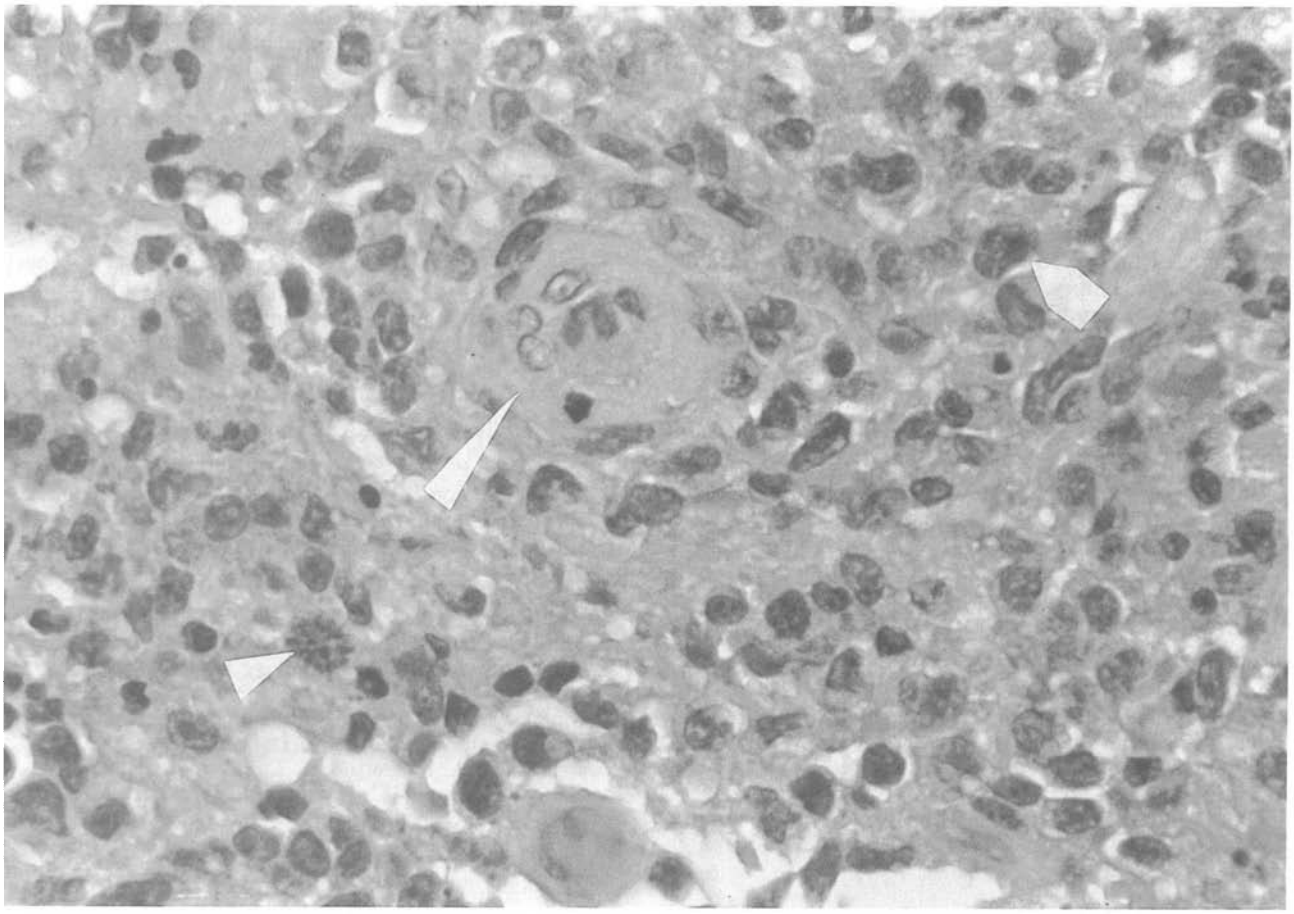

FIG. 2

Photomicrograph showing atypical lymphocytes with large cell immunoblastic phenotype. The small arrowhead indicates a mitotic figure, the large arrowhead a blood vessel, and the pentagon a typical lymphocyte. (H & E; × 80).

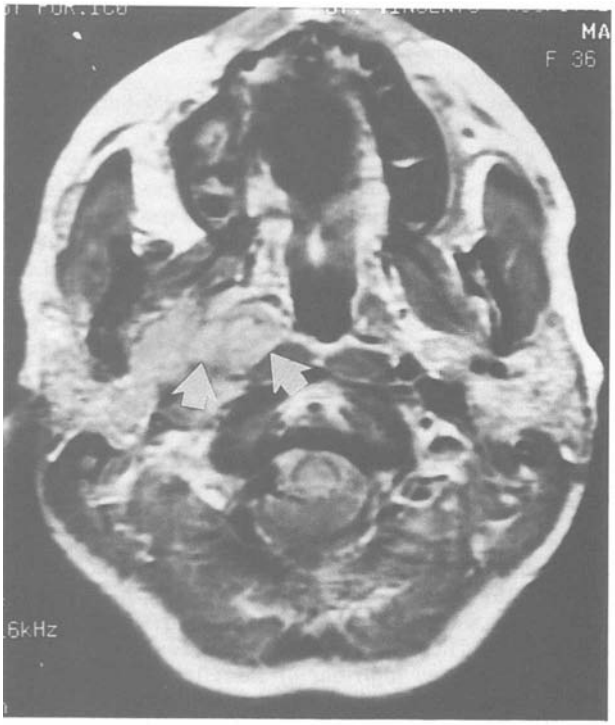

FIG. 3

MRI scan, T_1 without contrast. Arrows indicate the asymmetry of the right infratemporal fossa, and the effacement of the fossa of Rosenmuller.

NHL, develop the disease in extranodal sites, primarily the gastrointestinal tract (small bowel and anus) and the central nervous system (Beckhardt *et al.*, 1988; Ioachim, 1992; Jellinger and Paulas, 1992). The lymphomas are almost exclusively of the B-cell immunotype (Ioachim *et al.*, 1991). Of those developing NHL in the head and neck, Waldeyer's ring is a common site (Leess, 1987). In addition, reactive hypertrophied lymphoid tissue precedes lymphoma development in 30 per cent of the cases (Zurlo, 1992).

All groups at risk for HIV are at risk for developing a lymphoma, and the disease is similar as demonstrated by intravenous drug users, homosexual or bisexual men, haemophiliacs, and transfusion recipients (Levine, 1992). The Working Formulation for Clinical Usage has been widely applied for the histopathological staging of NHL (Ioachim *et al.*, 1991). The NHL of the HIV-positive patient is high grade, of B-cell origin, and is of the immunoblastic cell type or a small noncleaved lymphoma (Karp and Broder, 1991). The small noncleaved lymphoma may be further subclassified as 'Burkitt's' or 'non-Burkitt's' lymphoma. Approximately 80–90 per cent of patients are diagnosed with one of these subtypes.

A distinguishing feature of the AIDS lymphoma is the widespread extent of disease at presentation and the frequency of 'B' symptoms, including fever, drenching night sweats, weight loss in excess of 10 per cent of normal body weight. These symptoms have been seen in 82 per cent of systemic AIDS-related lymphoma and 91 per cent of those with central nervous system (CNS) disease. Patients present with extranodal disease from 68–84 per

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cent and 98 per cent as documented in a few large retrospective studies (Karp and Broder, 1991; Levine, 1992).

The reason for such unusually widespread extranodal disease in patients with AIDS or other immundeficiency states is unknown but may relate to perturbations of various adhesion molecules. Specifically LFA-1, and LFA-3 are down regulated in the neoplastic cells, often in association with c-myc gene expression.

Staging of the AIDS-related lymphoma should include bone marrow biopsy, total body CT, including chest, abdomen, pelvis and brain, gallium-67 scanning. Lumbar puncture is also indicated as 20 per cent of patients will have asymptomatic leptomeningeal disease (cytosine arabinoside or methotrexate is often instilled at the time of lumbar puncture as this has been shown to prevent CNS relapse). Specific radiographical analysis of the skull base should include MRI imaging with gadolinium.

In the non-HIV-related lymphoma shorter survival time is associated with increased tumour bulk, presence of systemic 'B' symptoms, and older age. In the HIV-related lymphoma prognostic indicators linked to decreased survival are the number of CD4 lymphocytes (Kaplan *et al.*, 1989), the diagnosis of AIDS prior to lymphoma occurrence, the extent of HIV-related disease, and the use of more intensive regimes of chemotherapy which have been found to worsen the already profound immunodeficiency. The following factors do not correlate with survival; leptomeningeal disease, mass size, elevated levels of lactic dehydrogenase (LDH), or systemic 'B' symptoms.

If left untreated, the average survival time will be about one month with death caused by the lymphoma. Non-Hodgkin's lymphomas are treated initially with low dose chemotherapy, sometimes in combination with radiotherapy. In cases with isolated disease, radiotherapy is appropriate (Goldberg *et al.*, 1993). Mean survival times are from four to six months. Extended survival to 1.5 years has been reported. In the event of relapse, no salvage therapy has been found to be helpful, even trials with bone marrow transplantation have been unsuccessful. Non-Hodgkin's lymphomas presenting in the head and neck are often recognized early and longer survival times may be observed.

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