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Oncology in Focus

Non-Hodgkin's lymphoma of the maxillary sinus in a patient with acquired immunodeficiency syndrome

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Abstract
Non-Hodgkin's lymphoma (NHL) is one of the most common malignancies in patients infected with human immunodeficiency virus (HIV); it occurs 25–60 times more frequently in HIV-infected patients than in the general population. This neoplasm in acquired immunodeficiency syndrome (AIDS) patients is a highly aggressive tumour with a poor prognosis and tends to develop in extranodal sites, such as the central nervous system, digestive tract and bone marrow. NHL involving the paranasal sinuses is rare in HIV-infected patients, and is likely to be confused clinically and radiographically with sinusitis; moreover, its optimal treatment is currently uncertain.

We present a case of NHL involving the left maxillary sinus in a patient with AIDS. The patient was treated with systemic chemotherapy (low dose-CHOP), but the malignancy did not respond. Subsequently, he was treated with local maxillary sinus irradiation which resulted in partial regression of the neoplasm and in decrease of local symptoms.

Key words: HIV; Lymphoma, non-Hodgkin's

Case report

A 50-year-old white male with severe haemophilia A, who had tested HIV-positive since 1985, was admitted to our hospital in June 1993. Zidovudine therapy had been administered between April 1990 and April 1993.

In August 1991, the patient had developed *Pneumocystis carinii* pneumonia and was treated successfully with trimethoprim/sulphamethoxazole; subsequently, secondary pneumocystis prophylaxis with trimethoprim/sulphamethoxazole was instituted. The patient was eventually lost to follow-up until 1993.

In April 1993, a painful, palpable mass overlying the left maxillary region was noted. The patient was admitted in another hospital where he underwent maxillofacial surgery to obtain a biopsy specimen. Pathological examination revealed a necrotic tumour within the left maxillary sinus which was consistent with a high-grade malignant, large-cell immunoblastic NHL of B cell origin (by the Working Formulation classification) (The non-Hodgkin's lymphoma Pathologic Classification Project, 1982); immunohistochemically, the tumour cells expressed CD20+, CD30+, CD45RO−. Examination of the biopsy specimen of the right maxillary sinus revealed only non specific chronic inflammation with fibrosis of the lamina propria. Examination of the cerebrospinal fluid (CSF), obtained via lumbar puncture, did not reveal presence of malignant cells.

On admission to our hospital in June 1993, the patient's temperature was 37.4 °C and Karnofsky performance score was 50. He had a painful facial swelling of the left maxillary region, extending inferiorly to the superior lip with skin paraesthesia. Physical examination revealed bilateral cervical lymphadenopathy.

On admission, laboratory tests revealed the following values: total white blood cell (WBC) was 1.30×10^9/L; polymorphonuclear neutrophil (PMN) count: 0.867×10^9/L; lymphocytes count: 0.234×10^9/L; CD4+ cell count: 6 mL; erythrocytes count: 3.08×10^{12}/L; the haemoglobin level was 8.2 g/dL; the platelet count was 182×10^9/L. Prothrombin time (PT), activated partial thromboplastin time (APTT) and serum levels of fibrinogen, urea nitrogen, creatinine, electrolytes, bilirubin, transaminase, lactic dehydrogenase, creatine phosphokinase were within the normal range. On admission, serological examination for fungi (particularly for *Aspergillus* spp., *Cryptococcus* spp. and *Candida* spp.) were negative; serology for antibodies to *Toxoplasma gondii* and for antibodies to cytomegalovirus (CMV) were positive: (IgM negative and IgG, respectively, 73 UI and >1/80).

Sinus radiographs revealed bilateral opacification of the maxillary sinuses. Computed tomography scan (CT) showed opacification of the left maxillary sinus, disruption of its anterior bone wall with swelling of the adjacent soft tissues and alteration of soft tissues of infrazygomatic fossae, infratemporal fossae and pterygomaxillary fossae; moreover, CT scan showed opacification of the right maxillary sinus with alteration of its anterior bone wall. CT scan of the head showed low grade cerebral atrophy, but

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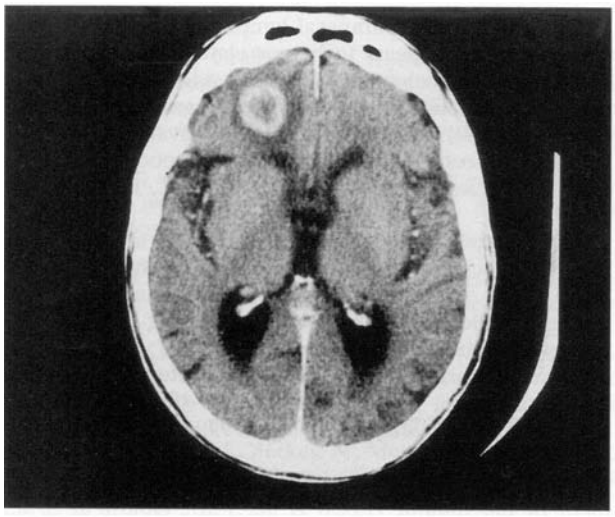

FIG. 1
Computed tomography scan shows a contrast-enhancing mass with oedema in the right frontal lobe.

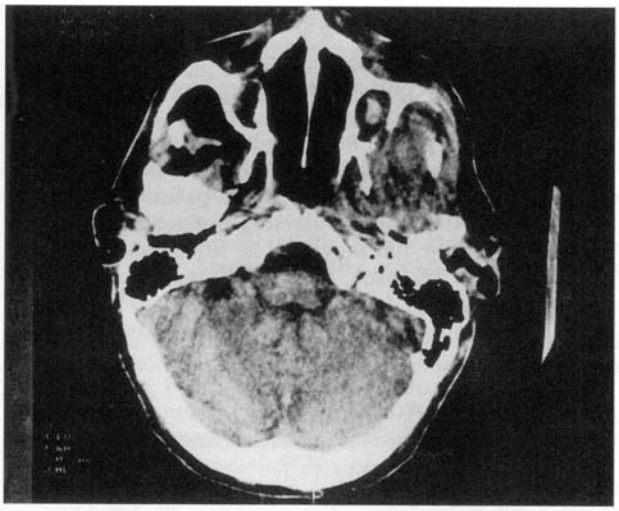

FIG. 3
Computed tomography scan shows partial decrease in size of left maxillary sinus infiltrating mass after local radiotherapy.

no other pathological findings. Echography and CT scan of the abdomen did not show any abnormality. Bone marrow biopsy revealed granulocytopoietic hypoplasia, erythroblastic hyperplasia with dyserythropoiesis and many plasma cells. CMV retinitis was diagnosed in the right eye and treated successfully with foscarnet.

On June 15, 1993, the patient received systemic chemotherapy consisting of cyclophosphamide (400 mg/m^2 i.v. day 1), doxorubicin (25 mg/m^2 i.v. day 1), vincristine (1.4 mg/m^2 i.v. day 1), prednisone (40 mg/m^2 p.o. days 1–5) and filgrastim (3 μg/Kg s.c. at day 6–21) (low dose-CHOP). Concurrently intrathecal methotrexate and prednisone were administered.

The lymphoma did not respond to chemotherapy: the patient quickly developed leucopenia with grade IV neutropenia (total WBC was 0.90×10^9/L and PMN count was 0.47×10^9/L) and two weeks after the antineoplastic cycle he showed increase in local facial swelling and severe continuous infraorbital pain which was treated with opioid and non-opioid analgesic drugs. On July 5, 1993, CT scan revealed a contrast-enhancing mass with oedema in the right frontal lobe (Figure 1) and an infiltrating mass of the left maxillary sinus (Figure 2). Examination of the CSF obtained via lumbar puncture revealed moderately low CSF glucose and moderately elevated CSF protein and evidence of few lymphocytes and histiocytes; all CSF cultures were negative. Serological examination for fungi and *Toxoplasma gondii* were repeated and results were similar to those upon admission to hospital.

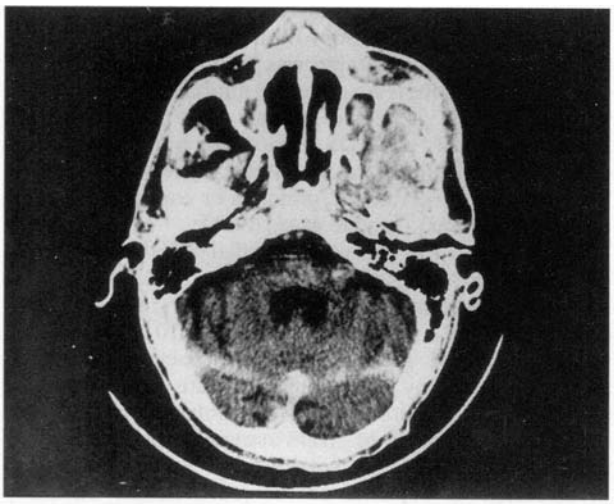

FIG. 2
Computed tomography scan shows infiltrating mass of the left maxillary sinus.

The patient was empirically treated for cerebral toxoplasmosis with pyrimethamine and sulphadiazine for 15 days; subsequently, magnetic resonance imaging (MRI) of the head showed increase in size, oedema and contrast-enhancing of the mass in the right frontal lobe. Failure of anti-toxoplasma therapy redirected the diagnosis to brain lymphoma. Brain biopsy was not performed as this was considered too great a risk in view of the patient being affected by haemophilia. MRI of the head revealed an increase in size of the infiltrating mass of the left maxillary sinus, which extended along the postero-infero-lateral bone wall and invaded the oral cavity, the masticatory space, the left infratemporal fossae and pterygomaxillary fossae; the mass had involved the pterygoid muscles and the caput profundum of the temporal muscle.

Radiotherapy was administered: because of the large extension of the malignancy it was decided to start with a local maxillary sinus irradiation and eventually to perform cerebral irradiation. Local radiotherapy of left maxillary sinus was performed with 23 fractions of 180 cGy per fraction to reach a total dose of 4140 cGy. After localized radiotherapy, facial swelling and clinical symptoms improved, and CT scan performed on August 28, 1993, revealed partial decrease of maxillary tumour (Figure 3). Subsequently, palliative cerebral radiotherapy was also instituted and was interrupted at a total dose of 2200 cGy. In the following days, the patient showed ideomotor slowing and deficit of cranial nerves.

The patient's clinical course was complicated by oral candidiasis, *Escherichia coli* and *Pseudomonas aeruginosa* urinary tract infections, *Pseudomonas aeruginosa* septicaemia, and by acute pneumonia. He died four months after the diagnosis of maxillary lymphoma. Autopsy was not performed.

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Discussion

NHL is common in patients with HIV-infection; previous studies reported an incidence of four to 10 per cent of the malignancy in these patients (Levine, 1987; Hamilton-Dutoit *et al.*, 1989). The frequency of this disease appears to be increasing in parallel to the increase of the average survival rate of HIV-infected patients (Shiramizu *et al.*, 1992). NHLs are apparently not restricted to any specific risk group, but they may be associated with some HIV-correlated diseases, such as Kaposi's sarcoma or persistent generalized lymphadenopathy. The majority of AIDS-associated NHLs are B-cell neoplasms (Ioachim *et al.*, 1991).

Epstein Barr virus (EBV) has been considered a possible agent of NHL because of its ability to immortalize B lymphocytes and because of its frequent association with the lymphomas that occur in immunocompromised non-HIV-infected persons (Pomilla *et al.*, 1995). In the pathogenesis of AIDS-associated NHL, it is likely that many other agents act as cofactors.

Although this malignancy in non-immunocompromised individuals occurs mostly in lymph nodes, in HIV-infected patients it tends to develop in extra-nodal sites, such as in the central nervous system, digestive tract and bone marrow (Bermudez *et al.*, 1989; Ioachim *et al.*, 1991). NHLs of the paranasal sinuses are rare: we have identified only 19 cases of NHL occurring in the paranasal sinuses of HIV-infected patients through a search up to 1996 of English-language articles (we have excluded cases involving the maxillary bone in which there was no apparent sinus involvement) (Leess *et al.*, 1987; Bermudez *et al.*, 1989; Quivey *et al.*, 1989; Schoem and Morton, 1990; Goldstein *et al.*, 1991; Ioachim *et al.*, 1991; Langford *et al.*, 1991; Desai *et al.*, 1992; Rosenthal *et al.*, 1992; Rubin and Sanfilippo, 1992; Shapiro *et al.*, 1992; Shiramizu *et al.*, 1992; Font *et al.*, 1993; Yang and Jayaram, 1993; Pomilla *et al.*, 1995).

Clinical symptoms in HIV-infected patients are similar to those reported in the general population affected by lymphoma involving the paranasal sinuses: local facial swelling, pain, skin paraesthesia and nasal discharge (Leess *et al.*, 1987; Schoem and Morton, 1990; Goldstein *et al.*, 1991; Desai *et al.*, 1992; Font *et al.*, 1993; Yang and Jayaram, 1993; Pomilla *et al.*, 1995). Initial signs or symptoms may be oral or ophthalmic (Langford *et al.*, 1991; Desai *et al.*, 1992; Rubin and Sanfilippo, 1992; Font *et al.*, 1993; Yang and Jayaram, 1993; Pomilla *et al.*, 1995); in some cases systemic symptoms may be present (such as fever or weight loss) (Leess *et al.*, 1987; Schoem and Morton, 1990; Pomilla *et al.*, 1995).

NHLs of paranasal sinuses have a tendency to invade adjacent structures, such as the orbit, pterygomaxillary fossae or oral cavity and sometimes they tend to disseminate to other sites (Leess *et al.*, 1987; Schoem and Morton, 1990; Langford *et al.*, 1991; Desai *et al.*, 1992; Rubin and Sanfilippo, 1992; Font *et al.*, 1993; Pomilla *et al.*, 1995).

Sinus radiographs usually show opacification, while CT and MRI show opacification, bone destruction, and invasion of adjacent structures (Leess *et al.*, 1987; Goldstein *et al.*, 1991; Langford *et al.*, 1991; Desai *et al.*, 1992; Rubin and Sanfilippo, 1992; Font *et al.*, 1993; Yang and Jayaram, 1993; Pomilla *et al.*, 1995).

Clinical and radiographical findings of paranasal NHL in AIDS-patients are similar to those seen in patients with sinusitis, a disease that occurs much more frequently in HIV-infected patients; therefore, an underestimation, or delay and error in diagnosis of paranasal NHL cases is possible.

The prognosis of paranasal lymphoma in immunocompetent subjects appears to be correlated with histological and immunohistochemical findings, stage, size, and systemic dissemination from the time of diagnosis (Cleary and Batsakis, 1994); with the data presently available, in HIV-infected patients the prognosis is very poor (Goldstein *et al.*, 1991; Langford *et al.*, 1991; Font *et al.*, 1993; Pomilla *et al.*, 1995).

The optimal treatment for NHL of the paranasal sinuses in HIV-infected patients is uncertain. Some physicians have used only chemotherapy, others only radiation therapy, while still others a combination of both chemotherapy and radiotherapy (Leess *et al.*, 1987; Quivey *et al.*, 1989; Schoem and Morton, 1990; Goldstein *et al.*, 1991; Langford *et al.*, 1991; Desai *et al.*, 1992; Rubin and Sanfilippo, 1992; Shapiro *et al.*, 1992; Font *et al.*, 1993; Pomilla *et al.*, 1995).

Multiagent chemotherapy may result in clinical improvement of the tumour (Leess *et al.*, 1987; Goldstein *et al.*, 1991), but it is often complicated by severe myelosuppression and neutropenia, resulting in increased risk of bacterial infections (Schoem and Morton, 1990; Goldstein *et al.*, 1991). The use of haemopoietic growth stimulating factors may help to prevent the HIV-associated infections. Some patients simply do not respond to chemotherapy (Leess *et al.*, 1987). Although the optimal chemotherapeutic regimen for NHL involving the paranasal sinuses remains undefined, the most frequently used protocol is CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), preferably associated with intrathecal methotrexate or cytosine arabinoside (Leess *et al.*, 1987; Goldstein *et al.*, 1991; Langford *et al.*, 1991; Desai *et al.*, 1992).

Local irradiation seems to be an effective modality for decreasing the severity of clinical symptoms and limiting local expansion of tumour (Quivey *et al.*, 1989; Goldstein *et al.*, 1991; Desai *et al.*, 1992; Rubin and Sanfilippo, 1992; Pomilla *et al.*, 1995). Following radiotherapy, patients may develop mucositis and oral opportunistic infections (Goldstein *et al*, 1991); these complications may be reduced by antifungal and antiherpetic prophylaxis and by maintaining adequate fluid intake and attending closely to oral hygiene (Goldstein *et al.*, 1991).

In conclusion, we believe that treatment should be individualized on the basis of the patient's general clinical condition, histochemical findings, size of neoplasm, and response to therapy. Our patient did not respond to chemotherapy, but responded successfully to local irradiation that resulted in partial regression of the maxillary NHL and in clinical improvement; perhaps his poor response to chemotherapy was due to less aggressive cytotoxic protocols; less aggressive antiblastic protocols are suggested in HIV-infected patients with poor prognostic factors (diagnosis of AIDS before lymphoma, low CD4+ cells, a Karnofsky performance status score of less than 70, bone marrow involvement, previous or concurrent opportunistic infections) (Levine *et al.*, 1991).

At the time of diagnosis of maxillary NHL, our patient presented poor prognostic factors: prior AIDS diagnosis, a Karnofsky performance score of 50, CMV retinitis, CD4+ cell count: 6/mL, PMN count: 0.867×10^9/L. Grade IV neutropenia and gram-negative septicaemia developed after chemotherapy. This clinical picture made it impossible to follow a more aggressive antiblastic protocol.

The clinical course of AIDS-associated paranasal NHL may be complicated by severe facial pain, also due to involvement of adjacent nerves (such as the maxillary branch of the trigeminal nerve and sphenopalatine ganglion). Patients should therefore also be treated with aggressive analgesic therapy, concomitantly with cytotoxic therapy.

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