

## Paranasal Sinus Involvement in Acute Lymphoblastic Leukemia

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Acute lymphoblastic leukemia (ALL) is a hemopoietic malignancy of the bone marrow that rarely invades the sinonasal area. If infiltration of paranasal sinuses occurs, it may lead to rhinosinusitis and orbital complications that need aggressive treatment. In this report, a 26-year-old male patient who had a history of ALL and had one relapse, suffered from rapid progression of right periorbital pain and exophthalmos, which usually presented in patients with orbital complications of sinusitis. A sinus computed tomography showed right maxillary and ethmoid sinus opacification with orbital bone destruction. Urgent endoscopic sinus surgery (ESS) was performed for orbital decompression and histopathologic diagnosis. Pathology revealed lymphoblast infiltration and inflammation of respiratory mucosa. Subsequent bone marrow aspiration cytology confirmed the diagnosis of a second relapse of ALL. Obstructive causes of sinusitis should be evaluated in patients with ALL. ESS has proven to be effective in obtaining tissue for histopathologic diagnosis, and in treating patients with sinusitis with orbital complications. (*Chang Gung Med J* 2004;27:924-9)

**Key words:** acute lymphoblastic leukemia, paranasal sinus, endoscopic sinus surgery.

Acute lymphoblastic leukemia (ALL) is a heterogeneous disease in which the malignant clone arises from lymphatic progenitors in the bone marrow or lymphatic system.<sup>(1)</sup> The diagnosis is made using morphology from bone marrow smears including cytochemistry, the detection of immunological markers, cytogenetic analysis and molecular genetic methods.<sup>(1)</sup> Extramedullary leukemic infiltration in the paranasal sinuses and nasal cavity is a rather rare event. We have managed some leukemia patients who suffered from acute rhinosinusitis during chemotherapy during the last decade but have never found leukemic invasion into the paranasal sinuses. Based on our research, only one case of childhood ALL with relapse involving the paranasal sinuses has been reported in the literature.<sup>(2)</sup> In the year 2000, we treated a patient who had a history of adult-onset

ALL with one previous relapse for acute rhinosinusitis and periorbital cellulitis.

### CASE REPORT

A 24-year-old Taiwanese man was found to have adult-onset ALL of T-cell lineage at the Chang Gung Memorial Hospital (CGMH) in July 1998. Initially, he complained of a 6-month history of dry cough, and a chest x-ray revealed a mediastinal mass. Histologic examination of the mass showed lymphoblast infiltration, and a cytologic examination of a bone marrow aspirate confirmed the diagnosis of ALL. A chemotherapy regimen consisting of daunorubicin, vincristine, L-asparaginase, and prednisolone (COAP) was subsequently carried out for 3 months, and triple intrathecal chemotherapy

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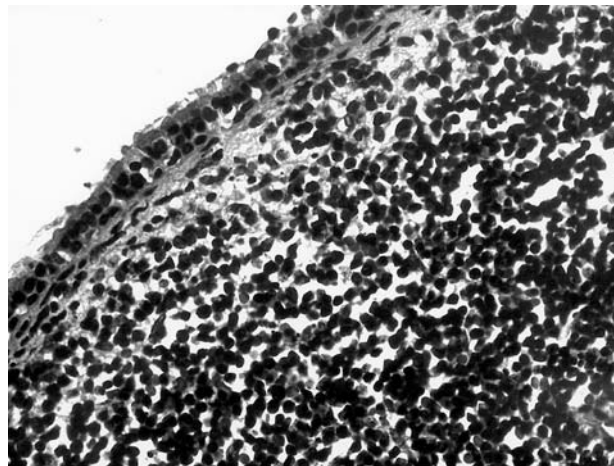
(methotrexate, cytarabine and hydrocortisone) was administered in three cycles. In November 1999, he returned to CGMH because of left cervical lymphadenopathy, and the first relapse was diagnosed after bone marrow aspiration cytology. A second course of chemotherapy using the same regimen as mentioned above was given for 6 months, after which a peripheral hemogram and cytologic examination of the bone marrow revealed a complete remission.

In June 2000, he visited Ear, Nose, and Throat outpatient department in CGMH with complaints of right cheek pain and swelling for 4 days, along with right nasal obstruction and purulent rhinorrhea for more than 4 months. Antihistamine and antibiotics were prescribed first. One week later, he suffered from right periorbital pain and exophthalmos which progressed rapidly within 2 days, and he was admitted to the hospital for further treatment. Physical examination showed right obliterated middle meatus, swollen inferior turbinate, red and swollen eyelids, and limited right eye movement (abduction and downward gaze), but no visual acuity or visual field deficits. The leukocyte count was  $12500 / \text{mm}^3$ , with 10 % normal and 6 % atypical lymphocytes and 84 % neutrophils and monocytes, and the platelet count was  $212000 / \text{mm}^3$ . A non-contrast-enhanced computed tomography (CT) scan of the paranasal sinuses revealed a right maxillary sinus lesion with erosion of the orbital bone and extension to the right orbit, right nasal vault (Fig. 1). Opacification of the right frontal and ethmoid sinuses was also noted.

Progression of exophthalmos and periorbital erythema was noted despite intravenous antibiotics treatment for 24 hours. In an attempt to treat the orbital complications and prevent damage to his vision and intracranial complications of sinusitis, we performed urgent ESS to decompress the orbital cavity, drain the sinus abscess, and obtain tissue for histopathological diagnosis. Diffuse inflamed mucosa with mucopurulent discharge from right middle meatus was observed during operation. The tissue obstructing the sinuses was partially removed piecemeal for orbital decompression. Histologic examination showed lymphoblasts with dense nuclei and scant cytoplasm diffusely infiltrating the submucosal tissue (Fig. 2). In addition, proliferation of the inflammatory cells was also noted. The diagnosis of a second relapse of ALL with infiltration of the right



**Fig. 1** Coronal computed tomography scan. An expansile lesion in the right maxillary sinus with erosion of bony walls and extension to the right orbit, right nasal vault.



**Fig. 2** Section of the maxillary lesion. Many lymphoblasts with dense nucleus and scant cytoplasm infiltrated into submucosal tissue. Hematoxylin and eosin stain.  $\times 200$ .

maxillary sinus was confirmed by bone marrow aspiration cytology. With antibiotic therapy and regular local debridement, symptoms of orbital complications completely resolved and purulent rhinorrhea subsided. He refused subsequent radiation therapy but agreed to a third course of chemotherapy for 7 months with a regimen consisting of vincristine, 6-Mercaptopurine, etoposide, daunorubicin, cyclophosphamide, cytarabine, indarubicin, and mitoxantrone.

Decreased visual acuity due to mild subhyaloid

hemorrhage of the right eye developed 3 months after the third course of chemotherapy, however, no significant disturbance of vision was noted. Opacification of the right sinuses was still noted on a follow-up CT scan 6 months after surgery (Fig. 3), but it did not cause any discomfort to the patient. He subsequently developed pneumonia and sepsis and died in March 2001.



**Fig. 3** Coronal computed tomography scan 6 months after surgery. Right maxillary and ethmoid sinus lesion without involvement of extraocular muscles.

## DISCUSSION

Acute lymphoblastic leukemia, a disease of the bone marrow pathophysiologically, represents a common form of childhood cancer but can occur at any age.<sup>(3)</sup> It is characterized by an abnormal clone of cells that have morphologic, biochemical, and immunologic characteristics of lymphoid cells.<sup>(3)</sup> Anemia, granulocytopenia, and thrombocytopenia are usually present at the time of diagnosis. ALL is confirmed by morphologic, cytochemical, and enzymatic stain analyses, together with the presence of 30% or more blasts in the bone marrow. The incidence in adults ranges between 0.7 and 1.8/1000000 per year with a second peak in adults older than 70 years.<sup>(1)</sup>

Clinically, ALL is recognized as a heterogeneous disease. Nevertheless, its extramedullary

metastasis to the paranasal sinuses and nasal cavity is a rather rare event. In a thorough autopsy survey of leukemia patients (4728 autopsy records), Viadana and coworkers found no extramedullary involvement in the paranasal sinuses or nasal cavity.<sup>(4)</sup> In their study, Sklansky et al. screened 273 acute leukemia patients. Leukemic cell infiltration was found in the head and neck regions in 88 patients, but they did not find any sinonasal involvement.<sup>(5)</sup> Lymphoma of the nasal cavity and sinuses was discussed relatively more often than leukemia. It is difficult to differentiate leukemia from lymphoma by clinical findings and histology, because both diseases may present as solid tumors showing lymphoblast infiltration of the paranasal sinuses or nasal cavity. Examination of the bone marrow is required to confirm the final diagnosis.

In addition to a thorough history and physical examination, imaging studies play important roles in the clinical decision making especially when the complications of sinusitis are suggested. In comparison with CT, plain films are less specific and sensitive in depicting the extent of sinus abnormalities. The primary advantage of CT is to depict bone and bone-air and bone - soft-tissue interfaces. The status of the bony walls of the sinuses is important both in benign sinus disease as well as sinus neoplasms.<sup>(6)</sup> Magnet resonance imaging (MRI) has become the imaging modality of choice in patients with complications of paranasal inflammatory disease, whether orbital, intracranial, or deep facial spread of an inflammatory process.<sup>(7)</sup> As to sinonasal tumors, MRI is superior in delineating the tumor from surrounding secretions, which are high signal on T2.<sup>(8)</sup> Only 5% of sinus tumors have high T2 signal (some minor salivary gland tumors, schwannomas, rare hemangiomas, and a small subgroup of inverted papillomas).<sup>(9)</sup> In this case, sinus CT showed a right maxillary sinus lesion with orbital extension and bone destruction. This correlated with the patient's symptoms and signs, thus, orbital complication of sinusitis caused by the sinus obstruction was diagnosed. Sinus malignancy is most likely to be the cause because of the osseous destruction showed on CT and the history of ALL with prior relapse. Due to persistent progression of the orbital complications despite antibiotic treatment, we decided to perform urgent endoscopic approach for orbital decompression and pathologic diagnosis.

Lusk et al. estimate that approximately 60% of orbital complications will require surgical intervention.<sup>(10)</sup> In a study by Bhargava and coworkers concerning the clinical progression of subperiosteal abscess as a serious complication of sinusitis, the criteria for operative intervention included progressive orbital cellulitis despite appropriate intravenous antibiotics for 48 hours, definite evidence of orbital subperiosteal abscess on a CT scan, and risk of loss vision and cavernous sinus thrombosis.<sup>(11)</sup> Schramm et al. suggested the following criteria for surgery including: (1) abscess formation, (2) visual acuity less than 20/60, (3) progression of disease for more than 24 hours, and (4) lack of resolution on antibiotics for 48 to 72 hours.<sup>(12)</sup> In general, treatment should be individualized and surgery should be considered when abscess is suggested or when the patient shows progression of orbital manifestations despite medical therapy. In our case whose exophthalmos and periorbital pain progressed even with intravenous antibiotics treatment for 24 hours, surgical intervention was indicated.

The main purpose of the ESS we performed was to eliminate orbital complications, treat the rhinosinusitis, and obtain tissue for histopathologic diagnosis. Stammberger described the successful management of not only sinusitis with periorbital cellulitis, but also cases with marked periorbital abscesses and even intraorbital abscesses with ESS.<sup>(13)</sup> Unilateral opacification of paranasal sinuses in the CT or MRI, especially in older patients, may be an indication for a neoplasm or mycotic sinusitis and therefore early histological diagnosis or operative treatment is strongly suggested.<sup>(14)</sup> In our patient whose CT revealed unilateral sinus opacification and orbital extension, malignancy should be taken into consideration and pathologic diagnosis was crucial. The endonasal endoscopic approach led to a successful pathologic diagnosis with minimal invasion as compared with surgical intervention via transbuccal antrostomy and external incision.<sup>(15)</sup>

Treatment for adult ALL patients includes intensive cyclic systemic chemotherapy, prophylaxis of central nervous system relapse, and bone marrow transplantation in distinct subgroups of patients.<sup>(1)</sup> Because extramedullary involvement of the paranasal sinuses and nasal cavity in leukemia is a rare event, there is no consensus on what constitutes the best treatment. In a retrospective study of 70

cases with sinonasal lymphoma, Logsdon and coworkers reported that those patients receiving the combined modality therapy (combination chemotherapy and radiation therapy) had more favorable prognoses than those who had radiation therapy alone.<sup>(16)</sup> As for the central nervous system and testicular relapse, the two most common forms of extramedullary relapse in ALL, local irradiation and chemotherapy were suggested to obtain prolonged periods of remission.<sup>(17)</sup> Regarding sinus relapse of ALL, we believe that chemotherapy combined with radiotherapy may be the better choice. However, our patient refused the radiotherapy that we suggested and only received chemotherapy.

Infections and hemorrhages have been the major life-threatening complications of patients with acute leukemia. Neutropenia and disruption of the normal mucosal barriers of the respiratory and gastrointestinal tracts are contributing factors to the high frequency of infections in leukemia patients.<sup>(18)</sup> Sinusitis is common in patients with leukemia and usually occurs when the patient is leukopenic, which in turn is frequently associated with chemotherapy or bone marrow transplantation.<sup>(19)</sup> Therefore sinusitis is commonly considered to be due to immunodeficiency in leukemia patients. Sinonasal tumors are frequently seen clinically as chronic sinus complaints. They often coexist with chronic inflammatory diseases and can be overshadowed by existent infection clinically.<sup>(9)</sup> Therefore, in leukemia patients with symptoms and signs of sinusitis, obstructive causes including malignancy should be considered and evaluated.

In summary, sinonasal involvement in ALL is a rather rare event that must be distinguished from lymphoma. Although immunocompromised patients with ALL have a high risk of infection, sinusitis cannot be regarded strictly as an infectious disease, and a complete evaluation for obstruction should be performed. ESS is effective in relieving sinus obstruction, treating orbital complications, and obtaining tissue for histopathology. Further studies are needed to determine the most effective treatment protocols.

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## 急性淋巴芽細胞白血病於副鼻竇腔的進犯

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急性淋巴芽細胞白血病是骨髓造血之惡性疾病，但在罕見的情況下，會進犯至鼻及鼻竇腔區域。此外，副鼻竇腔的進犯可能導致鼻竇炎及眼窩之併發症而需要更積極的治療。此病例為26歲男性病人，有罹患急性淋巴芽細胞白血病及一次復發的病史。病人發生進展快速的眼窩周圍疼痛及眼球突出等常見於鼻竇炎眼窩併發症的症狀，鼻竇電腦斷層檢查發現右側上頷竇及篩竇混濁性病灶合併眼窩骨破壞。經緊急內視鏡鼻竇手術施行眼窩減壓及組織切片檢查，病理報告顯示呼吸黏膜淋巴芽細胞浸潤，骨髓細胞學檢查證實急性淋巴芽細胞白血病第二次復發的診斷。急性淋巴芽細胞白血病病人之鼻竇炎需探查可能的阻塞原因，而內視鏡鼻竇手術可以提供組織病理學診斷，治療鼻竇炎及眼部併發症。(長庚醫誌2004;27:924-9)

**關鍵字：**急性淋巴芽細胞白血病，副鼻竇腔，內視鏡鼻竇手術。

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