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Isolated Gingival Relapse during Complete Hematological Remission in Acute Promyelocytic Leukemia

Many cases of acute leukemia with extramedullary involvement have been reported, and most of them are concomitant with bone marrow relapse. In the oral cavity, leukemic infiltrations of the dental pulp, mandible and tonsils were reported as isolated extramedullary relapses [1, 2]. Extramedullary recurrence in acute promyelocytic leukemia (APL) is very unusual in adults. To our knowledge, isolated gingival relapse during hematological remission in APL was reported in a previous case only by Sawatari et al. [3]. We report an additional case of APL associated with isolated gingival relapse during complete hematological remission.

A 19-year-old male patient was admitted to our hospital in January 1991 with fever, malaise, epistaxis and bloody otorrhea lasting for 1 month. Physical examination was normal except for petechial lesions on the lower extremities. No gingival swelling was found at that time. Anemia (Hb: 7.7 g/dl), thrombocytopenia (platelets: $24.0 \times 10^9/l$) and leukopenia (WBC: $1.9 \times 10^9/l$) were detected. Peripheral blood smear showed 55% blasts. Bone marrow aspiration was hypercellular with 68% atypical, hypergranular Auer rod positive promyelocytes. The tests for disseminated intravascular coagulation (DIC) were negative. Immunophenotypic studies showed CD13, CD33, and CD15 positivity together with negative HLA-DR antigen. A diagnosis of acute promyelocytic leukemia was established and therapy with aclarubicin 20 mg/m² and cytarabine 100 mg/m² was given. One month later, bone marrow examination with aspiration and biopsy was repeated and found to be in remission. Cytarabine 100 mg/m² for seven days was administered as consolidation therapy. Later, the patient was put on a maintenance therapy consisting of cytarabine 100 mg/m² intramuscularly and 6-thioguanine 100 mg/m² orally 5 days in a month for 3 months and then he was called for periodic controls without any treatment. In April 1992, he was readmitted because of gingival swelling. Physical examination revealed no change except for left upper gingival swelling. Cultures of the gingiva were obtained and revealed normal resident oral flora. Complete

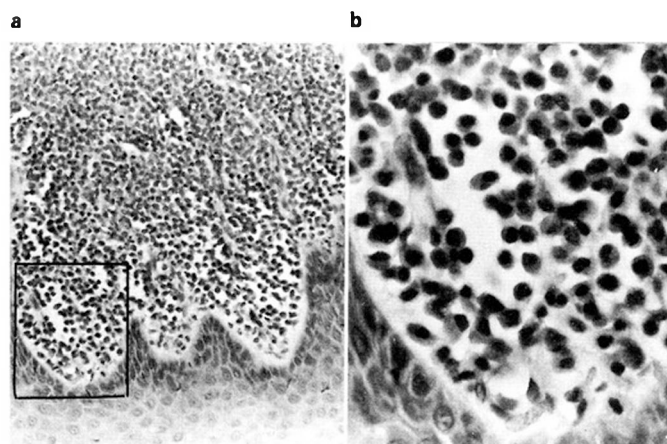


Fig. 1. Gingival relapse, granulocytic sarcoma infiltrating gingival submucosal tissue during complete hematological remission (**a** $\times 15$) and higher power view (**b** $\times 53$). HE.

hematological count was within normal limits. No evidence of leukemia was found on the examination of the peripheral blood smear, bone marrow aspiration and biopsy. A gingival biopsy specimen revealed diffuse leukemic infiltration. Microscopically, the nuclei of the malignant cells were hyperchromatic, multilobed and some of them were binucleated. The cytoplasm was eosinophilic and finely granular (fig. 1a, b). The presence of myeloid cells in the gingiva was also confirmed by chloroacetate esterase and Giemsa stains showing heavy azurophilic granulation. The gingival tumoral cells demonstrated myeloid surface antigens similar to his original disease. The patient refused chemotherapy or local radiotherapy. Six weeks later, he developed fever and pancytopenia and the gingival swelling persisted. This time the bone marrow was infiltrated with typical Auer rod positive promyelocytes. There were laboratory findings consistent with DIC. *Staphylococcus aureus*, coagulase positive was isolated from blood cultures. In spite of supportive therapy, he died of neutropenic sepsis and DIC in May 1992.

Extramedullary involvement, particularly of the gingiva, in APL is very unusual in adult patients and to date, there has been a single report [3]. Involvement of other extramedullary sites was not evident and no signs of central nervous system involvement were observed in this case or in our patient. Both patients had completed anti-leukemic therapy approximately 1 year before the gingival infiltration indicating a delayed form of relapse similar to that reported in the literature [2, 4]. These tumors may develop during the course of, or as a presenting sign of leukemia [4–7]. Rarely, however, extramedullary neoplasms composed of immature, poorly differentiated granulocytic precursor cells may occur without peripheral blood or bone marrow evidence of leukemia. Granulocytic sarcoma or chloroma is the term used for these localized, discolored soft tissue masses of leukemic infiltration [6]. Granulocytic sarcomas have a predilection for the cranium, bony orbit and facial bones. There have been previous reports of isolated relapses in the tonsils, mandible and dental pulp [1, 2]. Why the gingiva is one of the favored locations of relapse of acute leukemia still remains a mystery. Periodontal infections are particularly

common in leukemic patients and the migration of leukemic blasts as normal leukocytes to areas of inflammation may provide a reasonable explanation for this infiltration. Chronic periodontal disease may be the inflammatory stimulus underlying the gingival infiltrative hypertrophy [7]. Gingival cultures of our patient performed to rule out a possible chronic infection revealed normal resident oral flora.

Newer molecular techniques, including polymerase chain reaction (PCR), demonstrate that patients in morphologic remission of APL continue to have residual cells with the fusion gene product of the translocation (15; 17) [8]. The continued presence of this fusion gene indicates that such patients are likely to relapse. A positive result may be regarded as a strong indication for further treatment. Unfortunately, PCR studies could not be performed in our patient or in the other case reported by Sawatari et al. [3]. Bone marrow cytogenetic analysis and PCR may be important in patients with isolated extramedullary leukemic infiltrates to determine the patients' status and to predict the prognosis.

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