GRANULOCYTIC SARCOMA (CHLOROMA) OF THE ORAL CAVITY: A CASE WITH ALEUKEMIC PRESENTATION

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Granulocytic sarcoma (chloroma) of the oral cavity: A case with aleukemic presentation

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A case of granulocytic sarcoma, or chloroma, of the palatal mucosa, which developed 15 months before the onset of acute myelogenous leukemia (AML), is reported. The diagnosis was suspected on the basis of the light microscopic findings and confirmed by histochemical studies. Granulocytic sarcomas are rare, may be observed in a variety of body locations, and are considered specific lesions of AML or of the onset of blast crisis in chronic myelogenous leukemia. Primary granulocytic sarcomas of the oral cavity without systemic manifestations of AML are extremely rare. Clinical diagnosis of these lesions in patients with normal peripheral blood and bone marrow may be very difficult.
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Granulocytic sarcoma (GS), or chloroma, is a localized extramedullary tumor composed of immature cells of the granulocytic series.[1-5] The lesion was reported as long ago as 1811 and was termed *chloroma* because the tumor often exhibited a greenish color, resulting from the presence of myeloperoxidase (verdoperoxidase) in the tumor cells, that faded on exposure to the air.[1,4,6] The present term *granulocytic sarcoma* seems more appropriate because the tumor is not always green, is composed of immature cells of the granulocytic series, and resembles a sarcoma.[1,5]

Since the association of GS with acute leukemia was observed, more of these lesions have been reported in patients with acute myelogenous leukemia (AML) and also with the onset of blast crisis in chronic myelogenous leukemia.[1-5,7-11]

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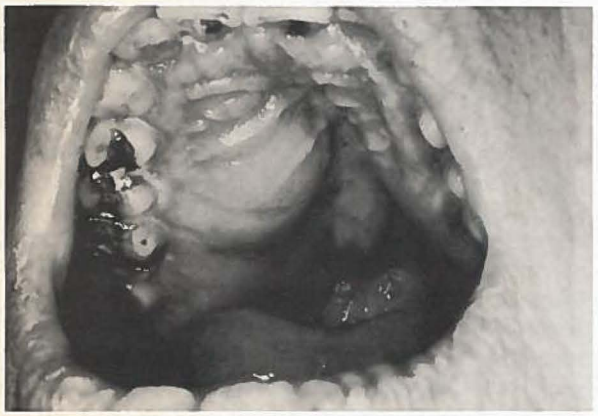

Fig. 1. Tumor mass in right palate was only slightly painful and was associated with occasional bleeding.

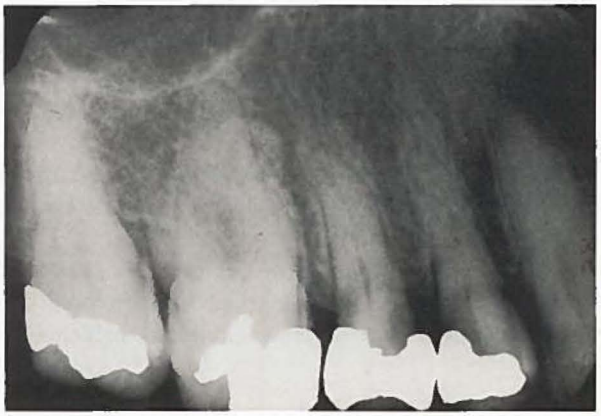

Fig. 2. Periapical radiograph of right posterior portion of maxilla showed no evidence of tumor infiltration.

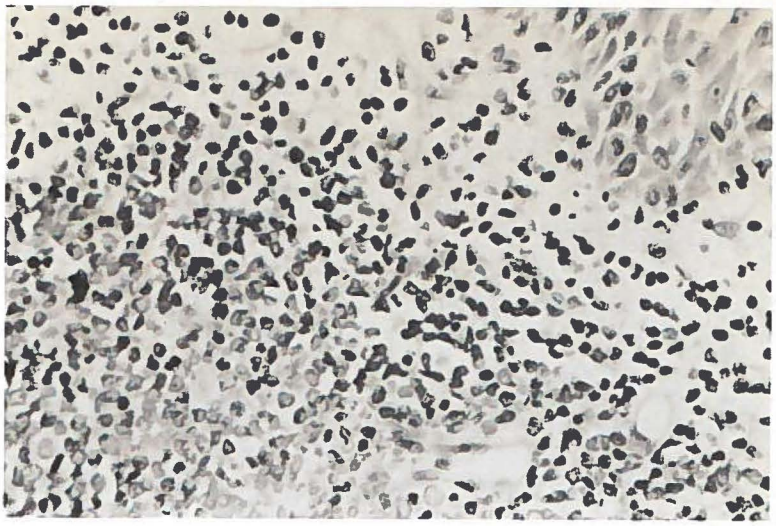

Fig. 3. Photomicrograph of tumor showing dense infiltrate of large round to ovoid cells in connective tissue. (Hematoxylin and eosin stain. Original magnification, ×100.)

Table I. Summary of eight cases of granulocytic sarcoma of the oral cavity

Source and Year	*Age*	*Sex*	*Location*	*Transformation to leukemia*	
				Type	*Elapsed time*
Brooks et al., 1974[10]	8	M	Right maxilla	AML†	4 years
Neiman et al., 1981[5]	NR*	NR*	Soft palate	NR*	—
Hansen et al., 1982[20]	83	F	Right maxilla	AML†	3 months
Takagi et al., 1983[21]	25	F	Left mandible	AML†	18 months
Reichart et al., 1984[22]	35	F	Right mandible	Promyelocytic	4 months
Castella et al., 1984[23]	89	F	Left hard palate	NR*	—
Welch et al., 1986[24]	3	F	Left maxilla	Not developed	—
Present case	67	F	Right palatal mucosa	AML†	15 months

*NR = Not reported.
†AML = Acute myelogenous leukemia.

Several reports of cases of GS that occurred in patients who displayed no detectable evidence of leukemia in the peripheral blood or bone marrow have been published.[2, 3, 12-19] GS may precede the manifestations of AML by months or years and can appear in a variety of sites including the skin, lymph nodes, bone, soft tissue, and visceral organs.[2, 5, 7-11, 13-19]

Only eight cases of GS localized in the oral cavity have been reported in the English language literature (Table I).

We report a case of GS of the mucosa of the hard palate that developed 15 months before the peripheral blood and bone marrow exhibited evidence of AML.

CASE REPORT

In November 1982, a 67-year-old white woman noted a mildly symptomatic swelling of the right side of the palate. She did not respond to hygiene procedures and antibiotics. Finally, she was referred for a biopsy in April 1983 (Fig. 1). The specimen was fixed in buffered formalin and submitted for histopathologic examination. The radiographic examination of the underlying maxilla did not show any bone destruction (Fig. 2).

The sections stained with hematoxylin and eosin consisted of loose connective tissue that contained a dense infiltrate of large round to ovoid cells with scant eosinophilic cytoplasm (Fig. 3). The nuclei were vesicular with prominent nucleoli, and many were hyperchromatic. Mitoses were numerous. The connective tissue was covered with normal squamous epithelium. A provisional diagnosis of extranodal malignant lymphoma was made, and the slides were submitted for consultation. One of the consultants suggested that the tumor was an infiltrate of leukemic blast cells and that special stains were needed. The paraffin-embedded sections were stained for chloroacetate esterase, and the tumor cells were strongly positive for the enzyme (Fig. 4). A final diagnosis of GS was made.

A complete blood count was normal. An iliac crest bone

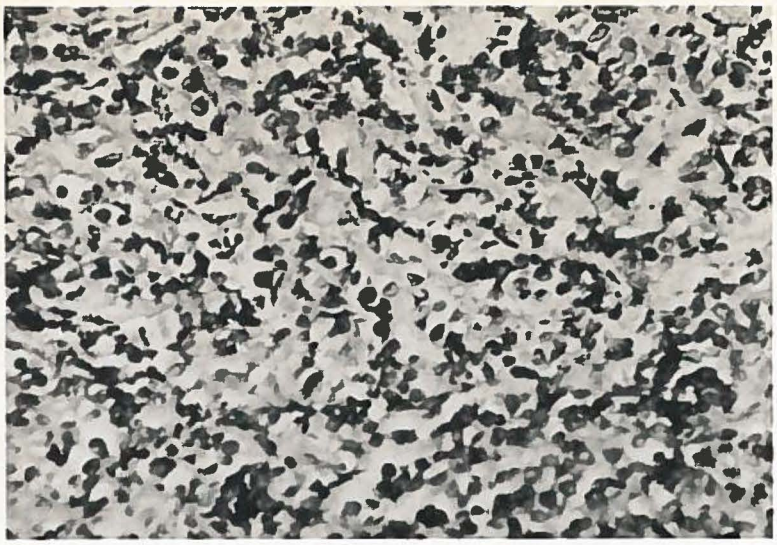

Fig. 4. Tumor cells stained with naphthol-ASD-chloroacetate. (Original magnification, ×100.)

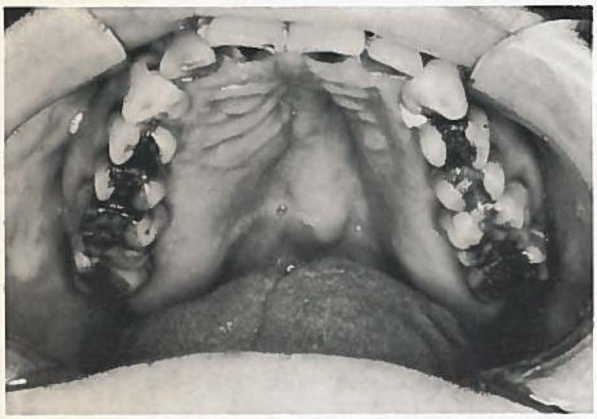

Fig. 5. Complete response of palatal tumor after radiation treatment.

marrow aspirate demonstrated a mild increase in the number of promyelocytes and mild erythroid dysplasia. A gallium scan showed a focus of increased uptake in the midportion of the face involving the right side of the maxilla and the nasal area. No other focal labeling abnormalities were noted.

In August 1983, treatment was started with the use of a 4 meV linear accelerator. The patient received a dose of 2340 rads (180 rads per day) in 13 fractions over 17 days. There was a rapid and complete reduction of the palatal mass (Fig. 5). In September 1983, a firm swelling of the left upper eyelid developed in the patient (Fig. 6). A greenish color was seen when the eyelid was everted. Over the next 3 months, the left lower eyelid also became involved. A presumptive diagnosis of GS was made, and the left eye was treated with 2400 rads in 12 treatments over 17 days. The lesions regressed completely. The blood

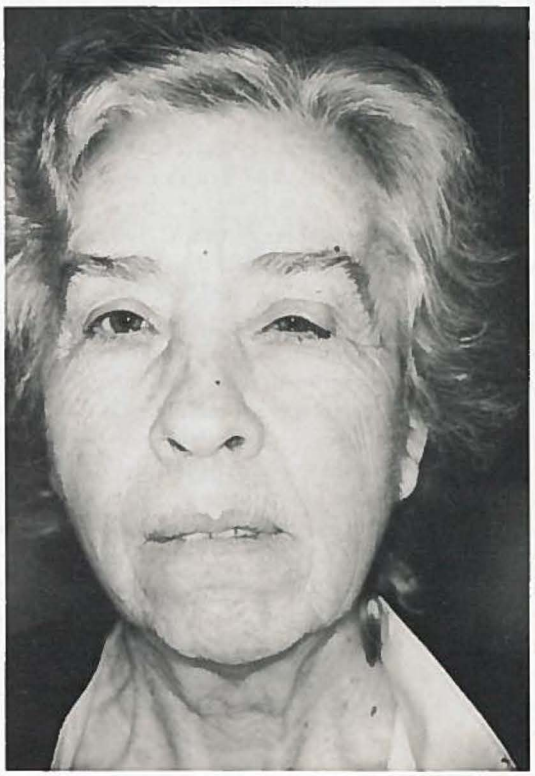

Fig. 6. Granulocytic sarcoma in left upper eyelid that developed 10 months after first tumor.

count remained normal, and a bone marrow examination showed no interval change.

The patient remained well until February 1984. At that time, she was seen again in the oral medicine clinic after experiencing dental discomfort. She also complained of

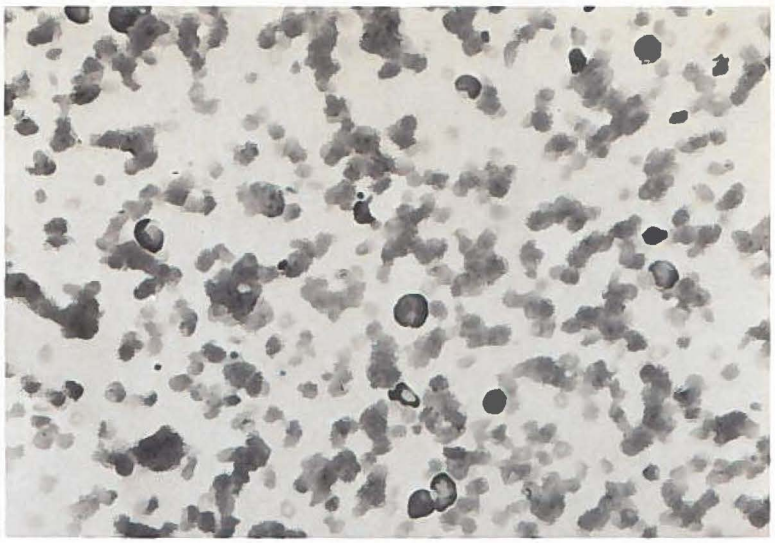

Fig. 7. Leukemic cells in bone marrow. (Wright-Giemsa stain. Original magnification, ×100.)

malaise, joint pain, and fever (up to 101° F) with chills. A blood cell count showed 20,000 white blood cells (granulocytes 14%, lymphocytes 13%, monocytes 2%, basophils 1%, blasts 66%); hemoglobin, 13.4 gm%; hematocrit, 38.5; and 124,000 platelets. The patient was hospitalized for further evaluation. A bone marrow biopsy showed infiltration of immature cells (Fig. 7), and a diagnosis of AML was made.

Cytotoxic induction therapy (ara-C 100 mg/m²/24 hr continuous intravenous drip for 7 days and doxorubicin 45 mg/m² for 3 days) was initiated. By March 1984, the patient felt well and an examination of the bone marrow revealed complete remission. In April 1984, she began her first consolidation treatment with ara-C and doxorubicin.

In early 1985, there was a simultaneous occurrence of abscessed teeth, fever, and malaise. A bone marrow evaluation revealed an exacerbation of the AML. Extractions of four abscessed teeth were complicated by thrombocytopenia, prolonged bleeding, and transfusion resistance from platelet destruction by host antibodies. Chemotherapy eventually led to control of the disease after several months. Subsequently, the patient was hospitalized several times because of relapses of the AML and for various induction and consolidation treatments. In November 1985, the patient died of internal bleeding and sepsis.

DISCUSSION

GS, or chloroma, has been described for many years as a localized tumor mass composed of immature myeloid cells; it is reported to be related to rare manifestations of both acute and, less commonly, chronic myelogenous leukemia. On rare occasions, GS may precede involvement of the peripheral blood and the bone marrow. While cases of isolated GS without the development of further hematologic abnormalities have been reported, the histopathologic diagnosis appears questionable because of the lack of special stains.[25,26] The elapsed time between the development of GS of the oral cavity (Table I) and the appearance of systemic manifestations ranged from 3 months to 4 years (mean, 17.6 months). Neiman and coworkers[5] reported on 61 biopsy-proven cases of GS, and 13 of 15 patients without systemic disease developed acute leukemia from 1 to 49 months (mean, 10 months) after the first diagnosis. Noteworthy is the case reported by Welch and colleagues[24] in which they observed GS of the maxillary sinus associated with extensive and highly destructive skeletal involvement. The clinical course of the disease was 3 years, and the patient never developed leukemia.

Our case further confirms that oral GS can precede the signs of AML in the peripheral blood and bone marrow by a prolonged period (15 months). It also demonstrates that the diagnosis of GS of the oral cavity may be very difficult and that GS can often be misdiagnosed.

The incidence of GS was reported to be 3% to 8% in two autopsy series of patients with AML.[11,27] Krause[12] observed an overall incidence of 28 cases (2.9%) of GS in 950 patients with AML or acute myelomonocytic leukemia, and 6 (0.6%) of these cases preceded development of acute leukemia. This tumor may occur in patients of any age, but it is often found in young people.[1,10] Liu and others.[11] reported 9 patients (39.1%) under 15 years of age in a group of 23 persons with GS. Variable symptoms and signs related to the involvement of the skeletal system and the soft tissues are very common.[5] While

the skull, vertebral and paravertebral area, sternum, and soft tissues of the chest wall are the most frequent sites, the orbit, oropharynx, nasopharynx, maxilla, mandible, salivary glands, and lymph nodes can also be involved.[5, 11]

When the bone marrow and/or peripheral blood examinations are within normal limits, the definitive diagnosis of GS may be extremely difficult with routine histologic techniques.[1, 5, 28, 29] The tumor cells may appear highly undifferentiated and mimic cells of amelanotic melanoma, lymphoma, alveolar rhabdomyosarcoma, or plasmacytoma.[1, 29, 30] Additional histochemical techniques, as well as electron microscopy, are necessary to identify the structure of the immature cells.[3, 21, 29-31]

In 1953, Gomori[32] first demonstrated that the substrate naphthol-ASD-chloroacetate produces an intense staining reaction in normal and neoplastic neutrophilic leukocytes. Subsequently, this enzyme stain with naphthol-ASD-chloroacetate as a substrate has been used for the visualization of an esterase specific for neutrophils, neutrophilic precursors, and mast cells.[31, 33, 34] Hydroperoxidase-positive phi bodies and rods described by Hanker and Romanovicz[35] are almost invariably observed in many of the immature cells of the granulocyte series in patients with AML.[36] They appear to be diagnostic of this disease and are present in about 92% of the patients.[29, 36] Electron microscopic evaluation of GS shows the presence in the tumor cells of uniform dense granules with a spherical or ellipsoid shape, which indicates the myeloblastic nature.[3, 21, 29] Recently, Welch and colleagues[24] reported on the diagnostic usefulness of monoclonal antibodies directed against myeloid cell surface antigens in determining the histogenesis and stage of maturation of GS.

The prognosis of GS is poor and strictly related to the clinical course of AML. The treatment of choice is local irradiation and chemotherapy.

REFERENCES

1. Rappaport H. Tumors of the hematopoietic system. In: Atlas of tumor pathology. Section III. Fascicle 8. Washington, D.C.: Armed Forces Institute of Pathology, 1966:241-3.
2. Wiernik PH, Serpick AA. Granulocytic sarcoma (chloroma). Blood 1970;35:361-9.
3. Mason TE, Demaree, RS Jr, Margolis CI. Granulocytic sarcoma (chloroma), two years preceding myelogenous leukemia. Cancer 1973;31:423-32.
4. Sears HF, Reid J. Granulocytic sarcoma: local presentation of a systemic disease. Cancer 1976;37:1808-13.
5. Neiman RS, Barcos M, Berard C, Bonner H, Mann R, Rydell RE, Bennett JM. Granulocytic sarcoma: A clinicopathologic study of 61 biopsied cases. Cancer 1981;48:1426-37.
6. Schultz J, Schwartz S. The chemistry of experimental chloroma. Cancer Res 1959;16:565-9.
7. Krishnamurthy M, Nusbacher N, Elguezabel A, Seligman BR. Granulocytic sarcoma of the brain. Cancer 1977;39:1542-6.
8. Gralnick HR, Dittmar K. Development of myeloblastoma with massive breast and ovarian involvement during remission in acute leukemia. Cancer 1969;24:746-9.
9. Kapadia SB, Krause JR, Kaubour AI, Hartsock RJ. Granulocytic sarcoma of the uterus. Cancer 1978;41:687-91.
10. Brooks HW, Evans AE, Glass RM, Pang EM. Chloromas of the head and neck in childhood. The initial manifestation of myeloid leukemia in three patients. Arch Otolaryngol 1974;100:306-8.
11. Liu PI, Ishimaru T, McGregor DH, Okada H, Steer A. Autopsy study of granulocytic sarcoma (chloroma) in patients with myelogenous leukemia, Hiroshima-Nagasaki 1949-1969. Cancer 1973;31:948-55.
12. Krause JR. Granulocytic sarcoma preceding acute leukemia. A report of six cases. Cancer 1979;44:1017-21.
13. Brugo EA, Larkin E, Molina-Escobar J, Costanzi J. Primary granulocytic sarcoma of the small bowel. Cancer 1975; 35:1333-40.
14. Hurwitz BS, Sutherland JC, Walker MD. Central nervous system chloromas preceding acute leukemia by one year. Neurology 1970;20:771-5.
15. Comings DE, Fayen AW, Carter P. Myeloblastoma preceding blood and marrow evidence of acute leukemia. Cancer 1965;18:253-8.
16. Belasco JB, Bryan JH, McMillan CW. Acute promyelocytic leukemia presenting as a pelvic mass. Med Pediatr Oncol 1978;4:289-95.
17. Long JC, Mihm MC. Multiple granulocytic tumors of the skin. Report of six cases of myelogenous leukemia with initial manifestations in the skin. Cancer 1977;39:2004-16.
18. Llena JF, Kawamoto K, Hirano A, Feiring EH. Granulocytic sarcoma of the central nervous system. Initial presentation of leukemia. Acta Neuropathol (Berl) 1978;42:145-7.
19. Seo IS, Hull MT, Pak HY. Granulocytic sarcoma of the cervix as a primary manifestation: case without overt leukemic features for 26 months. Cancer 1977;40:3030-37.
20. Hansen LS, Merrell PW, Bainton DF, Taylor KL. Granulocytic sarcoma: an aleukemic oral presentation. CDA J 1982;10:41-6.
21. Takagi M, Ishikawa G, Kamiyama R. Granulocytic sarcoma of the jaw. Bull Tokyo Med Dent Univ 1983;30:1-7.
22. Reichart PA, von Roemeling R, Krech R. Mandibular myelosarcoma (chloroma): primary oral manifestations of promyelocytic leukemia. Oral Surg Oral Med Oral Pathol 1984;58:424-7.
23. Castella A, Davey FR, Elbadawi A, Gordon GB. Granulocytic sarcoma of the hard palate: report of the first case. Hum Pathol 1984;15:1190-2.
24. Welch P, Grossi C, Carroll A, Dunham W, Royal S, Wilson E, Crist W. Granulocytic sarcoma with an indolent course and destructive skeletal disease. Tumor characterization with immunologic markers, electron microscopy, cytochemistry, and cytogenetic studies. Cancer 1986;57:1005-10.
25. Ragins AB, Tinsley M. Chloroma. Report of a case. J Neuropathol Exp Neurol 1950;9:186-92.
26. Washburn AH: Chloroma: report of a case with recovery following roentgenotherapy with review of the literature. Am J Dis Child 1930;30:330-48.
27. Muss HB, Moloney WC. Chloroma and other myeloblastic tumors. Blood 1973;42:721-8.
28. Laszlo J, Grode HL. Granulocytic leukemia and reticulum cell sarcoma. Cancer 1967;20:545-51.
29. McCarty KS Jr, Wortman J, Daly J, Rundles RW, Hanker JS. Chloroma (granulocytic sarcoma) without evidence of leukemia: facilitated light microscopic diagnosis. Blood 1980; 56:104-8.
30. Garfinkel LS, Bennett DG. Extramedullary myeloblastic transformation in chronic myelocytic leukemia simulating a coexistent malignant lymphoma. Am J Clin Pathol 1969; 51:638-45.

31. Leder LD. The chloroacetate esterase reaction. A useful means of histological diagnosis of hematological disorders from paraffin sections of skin. Am J Dermatopathol 1979; 1:39-42.
32. Gomori G. Chloroacyl esters as histochemical substrates. J Histochem Cytochem 1953;1:469-70.
33. Rozenszajn L, Leibovich M, Shoham D, Epstein J. The esterase activity in megaloblasts, leukaemic and normal haemopoietic cells. Br J Haematol 1968;14:605-10.
34. Yam LT, Li CY, Crosby WH. Cytochemical identification of monocytes and granulocytes. Am J Clin Pathol 1971;55:283-90.
35. Hanker JS, Romanovicz DK. Phi bodies: peroxidatic particles that produce crystalloidal cellular inclusions. Science 1977; 197:895-98.
36. Hanker JS, Amborse WW, James CH, Mandelkorn J, Yates PE, Gall SA, Bossen EH, Fay JW, Laszlo J, Moore JO. Facilitated light microscopic cytochemical diagnosis of acute myelogenous leukemia. Cancer Res 1979;39:1635-39.

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