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Unsuspected Gastric Granulocytic Sarcoma in a Patient with Myelodysplastic Syndrome

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Granulocytic sarcoma(GS) is an uncommon and localized extramedullary tumor composed of immature granulocytic cells. Most GS reported in large series were not associated with overt acute myelogenous leukemia. Gastric perforation occurred during prednisolone therapy in a 72-year-old Japanese male with a four-month history of a myelofibrosis-like state. Subtotal gastrectomy was performed for a suspected gastric ulcer perforation. Gastric histologic, immunohistochemical and cytochemical examination revealed diffuse infiltration by sheets of myeloblasts and promyelocytes with scant or moderately abundant cytoplasm including a few eosinophilic myelocytes. Bone marrow study done in one month after the operation disclosed refractory anemia with excess of blasts(RAEB). Leukemic transformation occurred two months later, and a subcutaneous tumor appeared on the forehead. The forehead tumor predominantly consisted of myeloblasts without evidence of maturation. Both the stomach and forehead tumors were examined immunohistochemically with a panel of monoclonal antibodies(LCA, L26, MT1, UCHL1, OPD4, LN-1, LN-2, LN-3, MB1, Leu-M1, PM) and polyclonal antibodies(lysozyme, α1-antitrypsin, α1-antichymotrypsin, S-100 protein, lactoferrin), as well as naphthol-ASD-chloroacetate esterase staining to investigate and characterize the reliable markes for GS, and the patient was diagnosed as GS. We found that gastric GS may occur in a myelofibrosis-like state followed by RAEB of myelodysplastic syndrome and that naphthol-ASD-chloroacetate esterase staining and immunohistochemical detection of MT1, lysozyme, and α1-antitrypsin were the most reliable markers for confirming the diagnosis of GS.

Key Words : *Granulocytic sarcoma, Myelodysplastic syndrome, Stomach*

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INTRODUCTION

Granulocytic sarcoma(GS) typically develops in three clinical settings ; 1) as a forerunner of acute myelogenous leukemia(AML) in nonleukemic patients, 2) as a sign of impending blast crisis in chronic myelogenous leukemia(CML) or leukemic transformation in myelodysplastic syndrome(MDS), and 3) as a tissue manifestation in patients with established AML(Neiman et al., 1981). There have been many case reports of GS in nonleukemic patients(Hurwitz et al., 1970 ; Mason et al., 1973 ; Brugo et al., 1977 ; Krause et al, 1979 ; McCarty et al., 1980 ; Neiman et al., 1981 ; Meis et al., 1986) but GS in a patient with MDS or myelofibrosis is very rare(Evans et al., 1990 ; Watanabe et al., 1990). GS can occur in any part of the body(Liu et al., 1973 ; Neiman et al., 1981 ; Petursson et al., 1981 ; Abeler et al., 1983 ; Castela et al., 1984 ; Meis et al., 1986 ; Ripp et al., 1989 ; Fellbaun et al., 1990 ;), but gastrointestinal GS is uncommon(Liu et al., 1973 ; Brugo et al., 1977 ; Neiman et al., 1981 ; Back et al., 1984 ; Meis et al., 1986 ; Wong et al., 1989).

GS can be divided into three groups based on the degree of granulocytic maturation : Group I(poorly differentiated) consisting of myeloblasts without maturation, Group II(moderately differentiated) consisting of an equal number of myeloblasts and promyelocytes, intermediate in maturation, and Group III(well differentiated) consisting of equal numbers of promyelocytes and myelocytes(Meis et al., 1986).

Initial diagnosis and differentiation from malignant lymphoma are often difficult in nonleukemic patients with GS(Neiman et al., 1981 ; Meis et al., 1986 ; Fellbaum et al., 1990). It is well known that naphthol-ASD-chloroacetate esterase(NASD) and lysozyme are good markers for confirming the diagnosis of GS(Neiman et al., 1981 ; Foucar et al., 1985 ; Meis et al., 1986).

This report describes the histopathologic, cytochemical and immunohistologic features of a gastric GS in a patient with a myelofibrosis-like state followed by refractory anemia with excess of blasts(RAEB) of myelodysplastic syndrome(MDS), together with GS arising in the subcutaneous tissue of the forehead after leukemic transformation from RAEB.

CASE REPORT

A 72-year-old Japanese male presented with a 4-year history of sporadic dizziness, loss of appetite and progressive emaciation. His medical history was unremarkable except for having suffered from viral hepatitis A and a mild degree of hypertension. He had had recurrent dizziness since February, 1986 but received neither specific examination nor treatment. Laboratory examination at that time revealed white blood cell count(WBC), 6,200/mm^3 ; red blood cell count(RBC), 306 × 10^4/mm^3 ; hemoglobin(Hb), 9.5g/dl ; hematocrit(Hct), 27.3 % ; platelet, 24.7 × 10^4/mm^3 ; serum iron, 46 μg/dl ; lactic dehydrogenase(LDH), 682 IU/l ; total protein(TP), 7.1 g/dl.

He was admitted for evaluation of the cause of his anemia, dizziness and elevated LDH level on April 7, 1990. Physical examination revealed a mild to moderate degree of splenomegaly, anemic conjunctiva, and severe emaciation. He was a native of Hiroshima Prefecture in Japan, who had lived there at the time of the atomic bomb explosion on August 6, 1945. Laboratory examination of peripheral blood(PB) at the first admission revealed WBC, 8,000/mm^3 with 2 % metamyelocytes, 16 % band forms, 63 % segmented neutrophils, 13 % lymphocytes, 1 % monocytes, and 5 % eosinophils ; RBC, 275 × 10^4/mm^3 ; 7.9 g/dl ; Hct, 25.5 % ; platelet, 21.7 × 10^4/mm^3. LDH was 815 IU/l(LDH1 : 20.7 %, LDH2 : 52.4 %, LDH3 : 18.1 %, LDH4 : 6.0 %, LDH5 : 2.8 %) ; CEA, 5.3 ng/ml ; AFP, 5.0 ng/ml ; ESR, 33/70 ; TP, 7.2 g/dl(AG ratio, 1.7). Bone marrow aspiration revealed a dry tap. An iliac bone biopsy was performed twice, which showed histological features consistent with myelofibrosis.

On June 18, 1990, laboratory examination of PB revealed WBC 7,100/mm^3 with 2 % myeloblasts, 1 % promyelocytes, 2 % myelocytes, 18 % band forms, 45 % segmented neutrophils, 16 % lymphocytes, 1 % monocytes, 3 % eosinophils, 3 % basophils, and 1 % eosinophilic metamyelocytes ; RBC, 225 × 10^4/mm^3 ; Hb, 6.78 g/dl ; Hct, 21.3 % ; platelet, 15.3 × 10^4/mm^3 ; LDH, 899 IU/l. A few megakaryocytes were present in the PB. From that time on, less than 5 % myeloblasts appeared consistently in the PB. The patient received prednisolone therapy(20 mg/day). He complained of epigastric pain, and endoscopic biopsies from the gastric fundus were performed twice. The endoscopic findings showed neither particular changes nor submucosal tumor mass in the posterior wall of the fundus, and the histological sections disclosed no pathological changes. He was discharged on July 26, 1990.

He was hospitalized again due to acute abdominal

pain on August 16, 1990. Laboratory data at the second admission were WBC, 5,600/mm^3 with 2 % myeloblasts, 1 % myelocytes, 3 % metamyelocytes, 16 % band forms, 57 % segmented neutrophils, 15 % lymphocytes, 2 % monocytes, and 4 % eosinophils; RBC, 267 × 10^4/mm^3 with tear drop-shaped erythrocytes; Hb, 8.5 g/dl; Hct, 27.4 %; platelet, 18.5 × 10^4/mm^3; LDH, 479 IU/l. A laparatomy revealed acute peritonitis of the posterior wall of the gastric fundus. A subtotal gastrectomy was performed under the clinical impression of gastric ulcer perforation. The stomach was diagnosed as moderately differentiated GS with perforation. Bone marrow aspiration cytology was unsuccessful, and the 3rd iliac bone biopsy was performed, which revealed the findings consistent with RAEB.

On November 21, 1990, laboratory examination revealed WBC 71,800/mm^3 with 72 % myeloblasts, 1 % myelocytes, 3 % metamyelocytes, 5 % band forms, 11 % segmented neutrophils, 8 % lymphocytes; RBC, 230 × 10^4/mm^3; Hb, 8.2 g/dl; Hct, 22.9 %; platelet, 9.8 × 10^4/mm^3; LDH, 910 IU/l. Myeloblasts in the PB did not show a tendency toward maturation, 20~30 % of them being myeloperoxidase-positive. Auer rods were not seen. He was diagnosed as having overt acute myelogenous leukemia and admitted on November 26, 1990. A tumor appeared on his forehead measuring 3.0 × 3.5 cm and was diagnosed as a poorly differentiated GS by needle biopsy. Serum lysozyme level was 63.6 μg/ml, and the karyotypic analysis from PB failed. The clinical summary and laboratory data are listed in Table 1. The patient received chemotherapy(adriamycin), but no remission was achieved. He died of acute respiratory failure due to pneumonia on April 13, 1991. Autopsy was not performed.

Table 1. Summary of Clinical and Laboratory Data of Case of Gastric Granulocytic Sarcoma in RAEB of Myelodysplastic Syndrome.

Data	1st admission ('90 Apr. 7.—Aug 1)						2nd admission (Aug. 16—Sep. 28)		3rd admission ('90 Nov. 26—'91 Apr. 13)				
	'90 Apr.		May		June		Aug.	Sep.	Nov.	Dec.	'91 Jan.		Apr.
	7	23	1	16	18	20	16	17	21	26	17	10	13
Biopsy													
Bone		*a)*				*b)*		*c)*					Death
Gastroscopic			*d)*	*e)*									
Forehead										*g)*			
Gastrectomy							*f)*						
LDH(IU/l)	815	708	807	827			479	672	910				
P.B													
WBC×10^3/mm^3	8	6.2		5.9	7.1	7.1	5.6	7.7	71.8	110	5.7	70.7	10.8
myeloblasts	0	0			2	4	2	2	72*h)*	86	13	84	79
promyelocytes	0	0			1	2	0	1	0	0	3	0	0
myelocytes	0	0			2	5	1	2	1	0	5	0	7
metamyelocytes	2	3			0	13	3	7	3	1	14	4	0
band forms	16	16			18	14	16	21	5	5	24	6	4
Seg. neutrophils	63	61			45	42	57	54	11	6	27	5	9
lymphocytes	13	17			16	14	15	7	8	2	12	1	1
monocytes	1	2			1	1	2	1	0	0	0	0	0
eosinophils	5	1			3	4	4	3	0	0	1	0	0
basophils	0	0			3	1	0	0	0	0	0	0	0
E. metamyelocytes	0	0			1	0	0	0	0	0	1	0	0
megakaryocytes	-	-			(+)	-	-	-	-	-	-	-	-
RBC×10^4/mm23	275	250		277	225	206	267	303	230	220	194	245	227
Hb(g/dl)	7.9	6.9		8.2	6.7	6.1	8.5	9.7	8.2	7.9	7.0	8.6	7.1
Hct(%)	25.5	22.9		25.6	21.3	19.6	27.4	31.3	22.9	25.2	20.4	24.8	21
platelet×1024/mm^3	21.7	22.2		18.5	15.3	15.8	18.5	14.8	9.8	11.1	3.0	2.0	2.2

a,b: Myelofibrosis, *c*: Refractory anemia with excess of blast cells, *d,e*: No pathological abnormalities are recognized,
f. Perforated gastric ulcer with peritonitis and granulocytic sarcoma, *g.* Granulocytic sarcoma,
h: Refractory anemia with excess of blast cells(RAEB) in transformation

MATERIALS AND METHODS

Tissue specimens from biopsies of the bone, stomach and forehead were fixed in 10 % buffered formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin, Giemsa, periodic acid-Schiff(PAS), Gomori's silver impregnation, methyl-green pyronin(MGP) and naphthol-ASD-chloroacetate esterase stain(Leder et al., 1964). For immunohistochemical staining, the peroxidase antiperoxidase(PAP) method(Sternberger et al., 1970) using polyclonal antibodies or the avidin-biotin complex(ABC) method using monoclonal antibodies(Hsu et al., 1981) was performed on deparaffinized sections.

Primary monoclonal antibodies used were leukocyte common antigen(anti-CD45RB + CD45, 1 : 25, Dakopatts/Denmark), MT1(anti-CD43, 1 : 20, Bio-Science/Switzerland), UCHL1(anti-CD45R, 1 : 25, Dakopatts/Denmark), L26(MX-Pan B, 1 : 100, Kyowa Medics/Japan), LN-1(anti-CDW45, prediluted by the manufacturer, Techniclon/USA), LN-2(anti-CD74, prediluted by the manufacturer, Techniclon/USA), LN-3(prediluted by the manufacturer, Techniclon/USA), OPD4(1 : 100, Dakopatts/Denmark), MB1 (anti-CD45RO, 1 : 20, Bio-Science/Switzerland), Leu-M1(anti-CD15, 1 : 20, Becton-Dickinson/USA), M1(anti-CD15, 1 : 100, Dakopatts/Denmark), and PM(MX-GMoA, anti-CD15, 1 : 25, Kyowa Medics/Japan).

Primary polyclonal antibodies used were against lysozyme(1 : 500, Dakopatts/Denmark), α1-antitrypsin(1 : 400, Dakopatts/Denmark), α1-antichymotrypsin(1 : 400, Dakopatts/Denmark), S-100 protein(1 : 1000, Dakopatts/Denmark), and lactoferrin(1 : 100, Dakopatts/Denmark).

PATHOLOGIC FINDINGS

Bone marrow

The first iliac bone biopsy disclosed fibrosing hypocellular marrow with increased reticulin fibers and focal hypercellular marrow with proliferation of myeloid, erythroid and megakaryocytic cell lines. In portions of hypercellular marrow, atypical megakaryocytosis were seen, but no evidence of particular morphological changes on the erythroid and myeloid precursor cells. Increased reticulin fibers were more frequently observed in areas of the hypocellular marrow(Fig. 1). The second bone biopsy showed marked hypocellu-

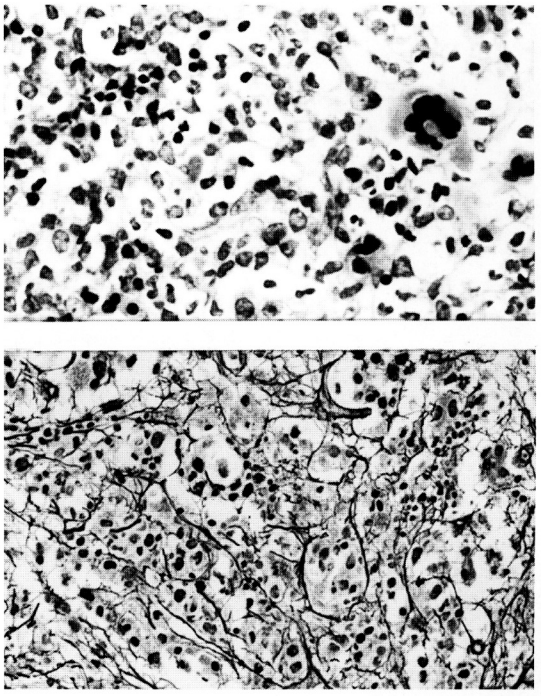

Fig. 1. The first iliac bone biopsy revealed focal hypercellular marrow with proliferation of myeloid, erythroid and megakaryocytic cell lines was observed. upper:(H&E), lower:(silver impregnation).

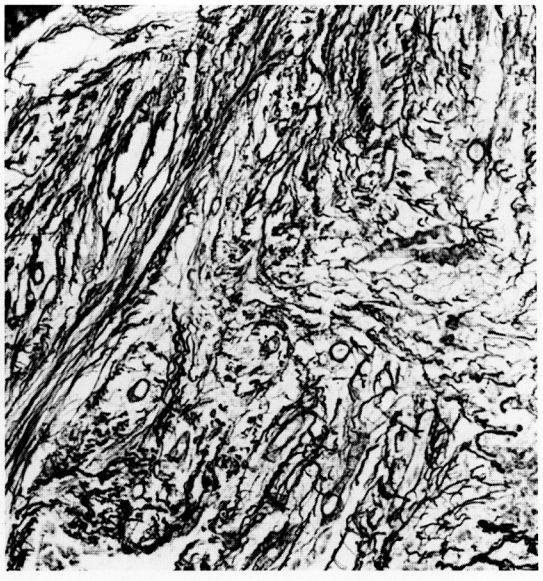

Fig. 2. The second iliac bone biopsy showed myelofibrosis with marked reticulin fiber production(silver impregnation).

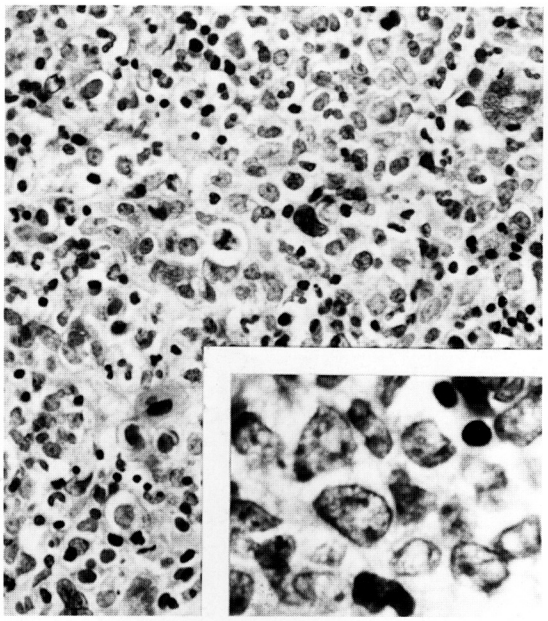

Fig. 3. The third iliac bone biopsy showed hypercellular marrow with abnormal proliferation of immature cells(H&E). Higher magnification of abnormal immature cells(inset).

lar marrow with severe fibrosis(Fig. 2). The third bone biopsy disclosed hypercellular marrow with clustering of myeloblasts(2 %) and promyelocytes, dyserythropoiesis and dysmegakaryocytopoiesis with fibrosis(Fig. 3), which was diagnosed as RAEB.

Stomach

The subtotally resected stomach exhibited an edematous gastric wall and smoothly elevated neoplastic tissue measuring 2.2 × 2.5 cm in the posterior wall of the fundus with a perforation measuring 0.5 × 0.4cm in the central portion of the tumor(Fig. 4). Histologic examination of the stomach revealed diffuse infiltration by clusters and sheets of immature cells in the submucosa, muscle coats and subserosal layers. The gastric mucosa overlying the tumor mass was apparently intact, but a few neoplastic cells positive for lysozyme and NASD infiltrated into the lamina propria and muscularis mucosae in focal areas of the ulcer margins. Heavy collections of the neoplastic infiltrates forming clusters were seen between bundles of muscle fibers(Fig. 5). The tumor cells had ovoid, irregular, or multilobated nuclei with one or two basophilic nucleoli and scant to moderate amounts of

Fig. 4. Stomach. Gastric mucosa overlying the granulocytic sarcoma was relatively intact except for the perforated margins(H&E).

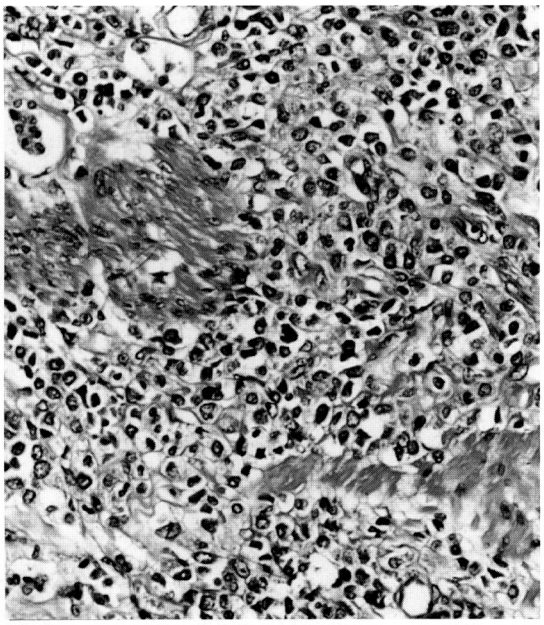

Fig. 5. Stomach. Heavy collections of granulocytic sarcoma cells were seen in the muscle layers(H&E).

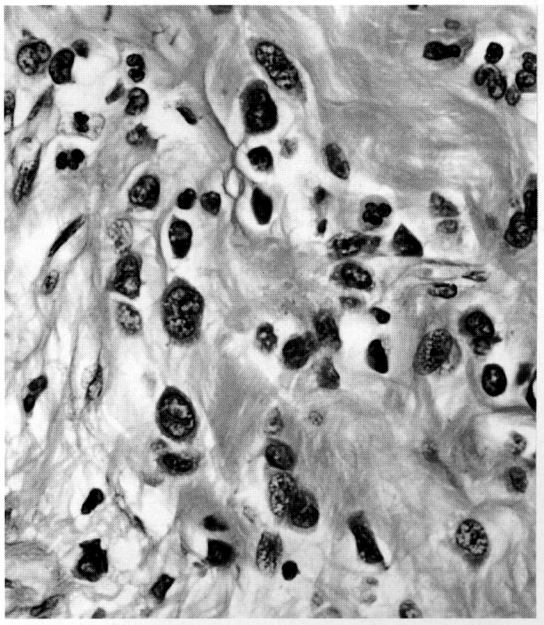

Fig. 6. Gastric granulocytic sarcoma cells showed moderate differentiation(H&E).

cytoplasm(Fig. 6). A large number of mitotic figures were observed. PAS reaction revealed weakly positive eosinophilic granulation of the cytoplasm. A few of the neutrophilic and eosinophilic myelocytes were seen in perivascular areas. About 85 % of the infiltrates exhibited cytoplasmic positivity for NASD(Fig. 7). Immunohistochemically, the tumor cells were strongly positive for lysozyme, LCA, α1-antitrypsin and MT1, and weakly positive for UCHL1 and α1-antichymotrypsin(Fig. 8). They were nonreactive with L26, LN-1, LN-2, LN-3, OPD4, MB1, S-100 protein, M1, Leu-M1, PM and lactoferrin. From this results of immunohistochemical and cytochemical stain indicate that the immature cells were myeloblasts and promyelocytes. A few scattered mature neutrophilic granulocytes showed positivity with L26, Leu-M1, M1 and lactoferrin. From these histological and immunohistochemical findings, this tumor was diagnosed as moderately differentiated GS.

Forehead tumor

The neoplastic tissue from the forehead consisted of myeloblasts without maturation. The tumor cells had round or oval nuclei with prominent and large nucleoli. The cytoplasm was scanty and had no eosinophilic granulation in the PAS reaction. Mitoses were infrequent. Eosinophilic myelocytes were not recognized.

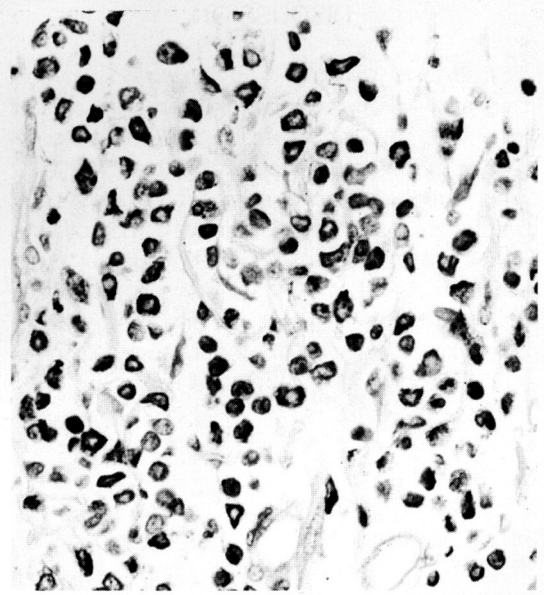

Fig. 7. The infiltrates of gastric granulocytic sarcoma showed strong positivity for NASD.

Fig. 8. The infiltrates of gastric granulocytic sarcoma showed strong positivity for lysozyme(Immunoperoxidase staining).

About 50 % of the infiltrates were positive for NASD. Immunohistochemical reaction of the tumor cells was almost the same as that of the gastric infiltrates.

DISCUSSION

Granulocytic sarcoma is an uncommon myeloid malignancy variant composed of immature cells of granulocytic precursors(Neiman et al., 1981 ; Meis et al., 1986). This tumor may be associated with AML, chronic myeloproliferative disorders including CML, myelofibrosis with myeloid metaplasia, polycythemia vera, and MDS(Neiman et al., 1981 ; Bennet et al., 1982 ; Wong et al., 1989 ; Evans et al., 1990 ; Watanabe et al., 1990 ;). The vast majority of GS in nonleukemic patients develop acute leukemia(Long et al., 1977 ; Krause et al., 1979 ; Neiman et al., 1981 ; Watanabe et al., 1990 ;), but some cases have been reported to reveal no leukemic manifestation (Beck et al., 1984 ; Meis et al., 1986 ;). Diagnosis of poorly differentiated GS in nonleukemic patients is extremely difficult. According to the medical literature, 56 % to 75 % of GS cases are initially misdiagnosed as malignant lymphoma, Ewing's sarcoma, malignant histiocytosis, synovial sarcoma or small cell anaplastic carcinoma(Neiman et al., 1981 ; Meis et al., 1986). Some special stains, particularly the NASD stain, provide a valuable tool for demonstrating the myeloid nature of the tumor cells (Moloneg et al., 1960). Before the development and use of the NASD stain in histologic sections, the presence of eosinophilic myelocytes stained with H & E or Giemsa was highly suggestive of GS. The intensity, frequency and distribution of the NASD reactions may vary greatly according to the maturity of the GS tumor cells(Castella et al., 1984 ; Meis et al., 1986). The specimens from the stomach and forehead of our case exhibited strong positive reactions for NASD ranging from 50 % to 80 %. Other special stains, including MGP, PAS and Giemsa were not helpful in confirming the diagnosis of granulocytic sarcoma. Immunohistochemical markers were helpful in confirming the diagnosis of GS. According to the reports of GS using immunohistochemical evaluation, the infiltrates of GS react with LCA, lysozyme, CD15, MT1, UCHL1, neutrophil granule protein elastase(NP57) and Ki-B3(Neiman et al., 1981 ; Meis et al., 1986 ; Muller et al., 1986 ; Davey et al., 1988 ; Fellbaum et al., 1990 ; Watanabe et al., 1990). Among the immunological markers, lysozyme, which is present in histiocytes and granulocytes (Greenberger et al., 1977), has been detected in a large number of tumor cells in all of the reported cases of GS(Neiman et al., 1981 ; Meis et al., 1986 ; Fellbaum et al., 1990). The present case showed strong positivity with LCA, lysozyme, MT1 and α 1-antitrypsin and weak positivity with UCHL1 and α 1-antichymotrypsin. It is interesting that α1-antitrypsin and α1-antichymotrypsin were positive in the infiltrates of both the stomach and forehead GS. In some cases, S-100 protein(Elliott et al., 1989) and CD15(Davey et al., 1988) have been positive in GS, but the presented specimens were negative. These cytochemical and immunohistological results indicated that the presented GS was a tumor of myeloid nature with granulocytic differentiation.

It has been reported that the degree of differentiation or maturation of tumor infiltrates of GS does not correlate with the development of AML or survival, and that mitotic rates do not correlate with clinical course and are highly variable both within and among cases(Meis et al., 1986). Moderate differentiation and high mitotic rates in the stomach and poor differentiation and low mitotic rates in the forehead featured these aspects in the present case.

Most nonleukemic patients with GS develop leuke-

mia, with a mean duration of 6 to 10.5 months, and die with a mean survival time of 8 months after diagnosis of GS(Neiman et al., 1981 ; Meis et al., 1986). According to the report of GS arising in the gastrointestinal tract(Brugo et al., 1977 ; Meis et al., 1986 ; Wong et al., 1989 ; Evans et al., 1990 ;) and uterine cervix(Meis et al., 1986), mucosal epithelial cells overlying the tumor are relatively well preserved. In the present case, gastroscopic biopsies were performed twice but neither diagnostic neoplastic infiltrates nor destruction of mucosal architecture was recognized. The gastric mucosa overlying the tumor tissue were relatively intact, but destroyed abruptly at the ulcer margins. This pattern of organ involvement of GS is distinctively different from that of malignant lymphoma. Malignant lymphoma is often associated with tissue destruction and coagulation necrosis within the tumor, whereas GS infiltrates tracts and tissue planes, preserving the tissue architecture without extensive destruction or tumor necrosis(Meis et al., 1986).

Idiopathic myelofibrosis is a chronic myeloproliferative condition characterized by massive splenomegaly, circulating erythroblasts and immature granulocytes, dimorphic erythrocytes with numerous teardrops cells, increased LAP scors, marrow fibrosis and often normal karyotype. In the present case, the first and the second bone marrow biopsy showed fibrosing hypocellular marrow with increased reticulin fibers which revealed histological features consistent with myelofibrosis, but laboratory findings of circulating bloods and physical examinations did not fit the myelofibrosis sufficiently.

Myelodysplastic syndromes are defined as a group of stem cell disorders characterized by maturation defects resulting in ineffective hematopoiesis and increased risk of transformation to AML. RAEB is a subset of MDS charactersized by less 5 % of circulating myeloblasts and 5 % to 20 % of myeloblasts in bone marrow(Bennet et al., 1982). The diagnosis of RAEB can be made only on a bone marrow aspirate by counting blasts, but the first and the second bone marrow aspirations were dry tap in spite of appearance of less 5 % of circulating myeloblasts in the present case.

According to the literature, 19 % to 64 % of RAEB patients have developed AML(Najean et al., 1977 ; Najean et al., 1979 ; Foucar et al., 1985 ; Oguma et al., 1986) and the median survival time of RAEB ranges from 7 to 13 months(Najean et al., 1977 ; Najean et al., 1979 ; Foucar et al., 1985 ; Kerkhofs et al., 1987). Our patient developed gastric GS after about 4 months of a myelofibrosis-like state prior to RAEB, forehead GS 6 days after the discovery of leukemic transformation in RAEB, and died about 4 months after the development of overt leukemia. The development of GS in patients with MDS devoid of leukemic transformation is very rare, and only a few cases have been reported(Evans et al., 1990 ; Watanabe et al., 1990).

MDS is basically a proliferative disorder and the majority of patients have hypercellular marrows, but a hypocellular marrow with increased reticulin fibers may be observed in MDS(Pagliuca et al., 1989), but is not a prominent finding. In the present case, hypocellular marrow with increased reticulin fibers, resembling a myelofibrosis-like lesion, was observed in the first and second iliac bone biopsy before the development of RAEB. Sultan et al reported that subset of MDS showing hypocellular marrow with increased reticulin fibers was often observed in patients with secondary MDS, and revealed poor prognosis(Sultan et al., 1981). The possibility of a secondary form of MDS due to previous exposition to radiation in this case was considered, but accurate information was not discernible.

In summary, the present case is a very rare case of gastric GS which appeared after four months duration of a myelofibrosis-like state prior to RAEB. It must be kept in mind that GS can also occur without leukemic transformation in MDS.

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