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CASE REPORT

Granulocytic Sarcoma with Severe Skin Involvement

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ABSTRACT

Acute myelogenous leukaemia typically involves intramedullary proliferation of myeloid precursor cells. Extramedullary manifestations of acute myelogenous leukaemia are rare. Granulocytic sarcoma, or chloroma, is one example of extramedullary leukaemia cells forming a mass in any part of the body. This report is of a healthy man who was diagnosed with acute myeloid leukaemia M5 (monocytic) with trisomy 8 and 11q23 chromosomal translocation. He developed severe skin nodules after cessation of consolidation therapy. He was treated with local radiation and had an excellent response.

Key Words: *Chromosomes, human, pair 8; Glutathione transferase; Leukemia, myeloid, acute; Translocation, genetic*

中文摘要

粒細胞肉瘤併發嚴重的皮膚病

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急性髓細胞性白血病一般涉及未成熟的髓樣細胞於髓內增生，很少累及髓外。粒細胞肉瘤又稱綠色瘤，是生長於髓外白血病細胞形成腫瘤的一個例子，可以累及身體任何部份。本文報告一名一向健康良好的男子，被確診為急性單核球髓樣白血病M5。他的第八對染色體出現三體症，並於第11對染色體長臂23位置（11q23）有易位。鞏固療法停止後，病人身上出現嚴重的皮膚結節。病人經局部放射治療後，療效良好。

INTRODUCTION

Granulocytic sarcoma (GS) is a localised solid collection of green-coloured tumour cells, which are essentially immature white blood cells, usually myeloid, associated with underlying myelogenous leukaemia. GS is commonly known as chloroma, from the Greek word 'chloros' meaning green.[1] Chloromas may be seen under the skin, around the eyes, or in the mouth; they can occur in multiple sites, such as the chest, vertebrae, pelvis, skin, lymph nodes, and skull. On rare occasions, chloromas can occur in the heart and brain. Chloromas are often painful.

CASE REPORT

A 65-year-old man was investigated in 2009 for anaemia. His white blood cell count was 8.7 x 10^9/l (reference range, 4.5-11.0 x 10^9/l) with 90% blast cells and 10% lymphocytes, and his haemoglobin level was 130 g/l (reference range, 140-175 g/l). Bone marrow aspirate showed 75% blast cells. These cells expressed trisomy 8 and 11q23 chromosomal translocation by fluorescent in-situ hybridisation. Flow cytometry revealed 87% of nucleated cells positive for CD34, CD117, bright CD64, HLAHRCD7, and CD4. This was consistent with acute myeloid leukaemia (AML)

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with M5 differentiation (monocytic). Nucleophosmin and feline murine sarcoma–related tyrosine kinase 3 were negative, showing karyotypically normal AML. Testicular ultrasound revealed a small hypoechoic lesion in the left testicle. Computed tomographic scan of chest and abdomen did not show any other abnormality but confirmed lesion in the left testicle.

The patient underwent induction chemotherapy with intravenous daunorubicin 50 mg/m^2 for 3 days and subcutaneous cytarabine 100 mg/m^2 for 7 days (7 + 3 regimen) in August 2009. Bone marrow biopsy on day 14 showed that the treatment failed to achieve remission. He was given a second cycle of daunorubicin and cytarabine chemotherapy, and achieved remission. Subsequently, he received testicular radiation at a dose of 24 Gy in 12 fractions, using a 6-MV photon beam, with the first cycle of consolidation chemotherapy in October 2009. A few weeks after reinduction chemotherapy, he developed cardiac myopathy secondary to anthracycline-based chemotherapy and was switched to subcutaneous cytarabine with palliative intent in late October 2009.

He developed cutaneous involvement 2 months after cessation of systemic treatment. The lesions were predominantly on the abdominal wall and left forearm. At examination, these lesions were 1 to 2 cm in size and non-confluent. Biopsy was obtained from a skin lesion on the left forearm, which revealed dense infiltrate by medium-to-large cells with round nuclei, vesicular chromatin, single prominent nucleoli, and scant cytoplasm. There was significant crush artefact. Scattered mitoses were noted. Immunohistochemical staining revealed that most of the cells were positive for CD34 and CD68, but negative for myeloperoxidase, CD117, CD3, and CD20. The morphological features and immunoprofile were in keeping with GS, an extramedullary manifestation of AML (Figure 1). The lesions were firm, itchy, ulcerating, bleeding, and crusty (Figure 2). Palliative radiation to the skin lesions was planned to be delivered by a 160-kV superficial photon machine. The patient declined a long fractionation schedule of 30 Gy in 10 fractions, 8 Gy in a single fraction was delivered. Four weeks postradiation, all the areas receiving radiation showed a good response and were asymptomatic (Figure 3). Restaging computed tomographic scan did not show any visceral involvement. The patient had a massive stroke 6 weeks after completion of radiotherapy and died of apnoea.

DISCUSSION

Myeloid sarcoma (chloroma, GS, extramedullary

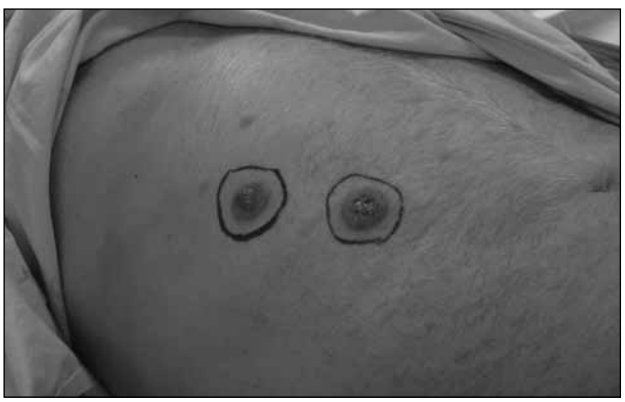

Figure 2. Ulcerating lesions on the anterior abdominal wall.

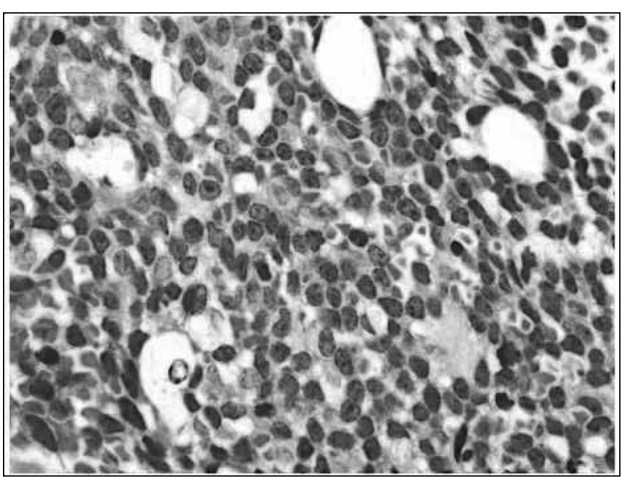

Figure 1. Microphotograph showing immature blast cells (haematoxylin and eosin stain; original magnification, x 100).

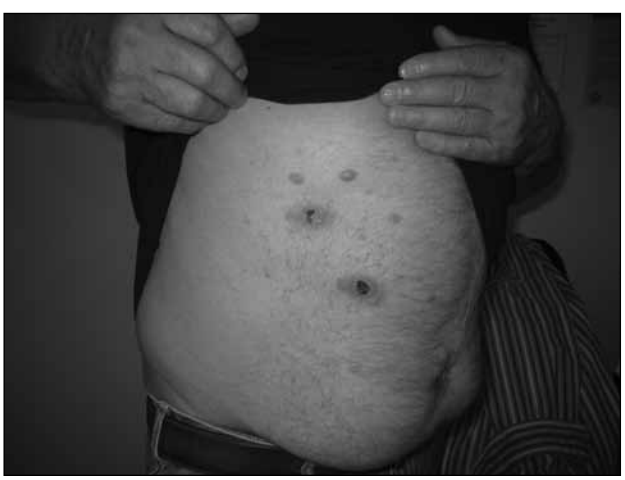

Figure 3. Lesions on the anterior abdominal wall 4 weeks postradiation.

myeloid tumour) is a solid neoplasm, which is usually composed of immature white blood cells such as myeloblasts. This tumour was first reported in 1811.[2] As these tumours are often greenish in colour due to the enzymatic action of myeloperoxidase in the tumour cells, the term 'chloroma' was given to this lesion in 1853.[3] Myeloid sarcoma is an extramedullary manifestation of AML. Infiltration occurs most commonly in patients with the monocytic subtypes of AML. A predisposing factor could be polymorphisms of enzymes that metabolise carcinogens, but this is inconclusive.[4] Definitive diagnosis of a chloroma usually requires histological confirmation of the lesion. Historically, even with a tissue biopsy, pathological misdiagnosis has been an important problem, particularly among patients without a clear pre-existing diagnosis of AML to guide the pathologist. In modern medicine, with the help of advances in diagnostic techniques, the diagnosis of chloroma can be made more reliably.[5]

Traweek et al described the use of a commercially available panel of monoclonal antibodies against myeloperoxidase, CD68 (cluster designate), CD43, and CD20 to differentiate it from other haematological malignancies such as Hodgkin's lymphoma, Burkitt's lymphoma, large-cell lymphomas, and small round blue cell tumours such as neuroectodermal tumours.[6] Additionally, one or more of the markers indicative of a myeloid origin are usually positive: lysozyme, CD13, CD14, CD33, CD34, CD68, and CD117. CD13, CD14, and CD33 are only available for frozen sections, while CD117 is also positive for gastrointestinal stromal cell tumours. Therefore, positive staining of a combination of markers (CD34, CD43, CD4, MPO, lysozyme, glycophorin C) together with compatible morphology is considered diagnostic. Positive CD43 staining is important for diagnosing GS, especially when other myeloid markers such as myeloperoxidase do not always stain.[7]

The use of flow cytometry has also helped clinicians to accurately diagnose these lesions.[8] GSs may develop during the course of, or as a presenting sign of, myelogenous leukaemia. Less frequently (in up to 35% of patients), GSs may precede the haematological leukaemia by months or years and can, therefore, be difficult to differentiate from lymphoma clinically, radiologically, and pathologically. Special staining and modern histochemistry studies are required for accurate diagnosis. A small series of GSs or 'chloromas' has been studied by means of conventional histology and immunohistochemistry. The latter was found to be most useful for the diagnosis and characterisation of these tumours.[9] No prognostic significance exists between acute leukaemia patients with GSs and those without. However, patients with GSs who have chronic leukaemia or myeloproliferative disorders have a poor prognosis, because these tumours often occur during acute transformation.[10]

The World Health Organization has classified GS into 3 main types, depending on the degree of maturation: blastic, composed mainly of myeloblasts; immature, composed of myeloblasts and promyelocytes; and differentiated, composed of promyelocytes and mature myeloid cells.[11]

Large clinical reviews suggest that the most common locations for chloroma are the skin, bone, soft tissues, and lymph nodes.[12] Patients usually present with a history of AML. On rare occasions, a patient will be diagnosed with chloroma without a primary diagnosis of AML, but almost all of these patients went on to develop AML within 2 years.[13]

Treatment for chloromas consists of systemic chemotherapy for the underlying leukaemia, and the lesions frequently respond well. When urgent decompression is needed, or if the lesion is refractory to systemic chemotherapy, surgical debridement or radiation therapy may be considered. The response to systemic therapy is greater for patients presenting with new-onset AML than for those with relapse.[10] GSs are sensitive to local irradiation. The optimum radiation dose and fractionation is not known. The commonly used fractionation ranges from 20 Gy in 5 fractions to 40 Gy in 20 fractions. The lesions generally resolve completely in less than 3 months with any fractionation schedule, although they recur in approximately 23% of patients.[14] In this patient, the skin lesions responded to radiation, but he developed more lesions in other sites although they were asymptomatic. There is conflicting evidence on the prognostic significance of chloromas in patients with AML. In general, chloromas are thought to augur a poor prognosis, with a poor response to treatment. However, some authors have reported that chloromas associate, as a biologic marker, with other poor prognostic factors, and therefore do not have independent prognostic significance.[15]

Patients treated for AML who relapse with skin manifestations are typically treated with systemic chemotherapy for relapsed leukaemia. However, the outcome is usually poor. Chloromas are typically sensi-

tive to standard systemic chemotherapy. Therefore, if the chloroma is persistent after completion of induction chemotherapy, as for this patient, local treatment such as surgery and radiation can be explored as an option. Most patients will have a good local response.

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