CASE REPORT

Granulocytic sarcoma in a patient with chronic myeloid leukaemia in complete haematological, cytogenetic and molecular remission

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SUMMARY

Granulocytic sarcoma, also known as myeloid sarcoma, is an extramedullary tumour composed of immature myeloid cells. Granulocytic sarcoma is typically found in patients with acute myeloid leukaemia, accelerated phase or blast crisis of chronic myeloid leukaemia, myelodysplastic syndrome, or as an isolated event without bone marrow involvement. We present a case of granulocytic sarcoma in a patient with chronic myeloid leukaemia in the setting of complete haematological, molecular and cytogenetic remission. Our patient was first treated with imatinib for chronic-phase chronic myeloid leukaemia. After maintaining remission for 42 months, he developed a granulocytic sarcoma in his spine. In this case report, we describe our case, along with the three other cases reported in the literature. In addition to being a rare diagnosis, this case demonstrates the importance of being vigilant in diagnosing the cause of back pain and atypical symptoms in patients with a history of leukaemia.

BACKGROUND

Granulocytic sarcoma (GS), also known as myeloid sarcoma, is an extramedullary tumour composed of immature myeloid cells.¹ GS has been cited to occur in 2.5–9.1% of patients with acute myeloid leukaemia (AML),^{1–2} accelerated phase or blast crisis of chronic myeloid leukaemia (CML), myelodysplastic syndrome (MDS) and as an isolated event without bone marrow involvement.^{2–4} We present a case of GS in a patient with CML in the setting of a complete haematological response (CHR), a major molecular response (MMR) and a complete cytogenetic response (CCyR), which, to the best of our knowledge, represents the fourth case reported in the medical literature.

CASE PRESENTATION

A previously healthy 30-year-old white male presented to his primary care physician with a 4-month history of fatigue. Review of systems was positive for dyspnoea on exertion, chills, subjective fevers and sweats, and negative for headache, back pain, bone pain or any neurological deficits. Physical examination was unremarkable except for palpable splenomegaly extending to the left iliac crest. Complete blood count showed 315 000 white cell counts with 3% blast cells, 10% promyelocytes, 19% myelocytes, 18% metamyelocytes and 19% neutrophils. Haemoglobin was 7.3 g/dL and platelet count was 181 000. Leucocyte alkaline

phosphatase score was 3 and lactate dehydrogenase level was elevated to 5111 U/L. The patient's subsequent work up included karyotype analysis and flow cytometry of the peripheral blood, reverse transcription PCR (RT-PCR) for BCR-ABL, and a bone marrow aspirate and biopsy. No imaging was indicated at this time. The patient was started on cytoreductive therapy with hydroxyurea, tumour lysis prophylaxis, and was transfused with 3 units of packed red blood cells.

The RT-PCR for BCR-ABL gene rearrangement of the peripheral blood returned positive and cytogenetics showed a 46,XY,t(9;22)(q34;q11.2) karyotype. The patient's bone marrow biopsy showed a hypercellular marrow with marked, left-shifted granulocytic hyperplasia and a FISH analysis was positive for the BCR-ABL rearrangement. There were less than 5% blasts present in the aspirate and the diagnosis of chronic-phase CML was made. Hydroxyurea was discontinued and oral imatinib 400 mg daily was initiated. Within 3 months of starting imatinib, CHR was achieved. A bone marrow aspirate that showed CCyR, as well as MMR, was documented 1 year from initiation of therapy with imatinib. Repeat cytogenetic and FISH testing on a bone marrow aspirate and biopsy were negative for t(9;22) and BCR-ABL, respectively, indicating CCyR and complete molecular response (CMR). CCyR, CMR and CHR were maintained on imatinib therapy for another year.

Twenty-five months after the diagnosis of CML, the patient developed lower back pain. A bone scan and MRI showed an "enhancing soft tissue mass in the para-spinal regions from T5 to T8 (right > left). There was involvement of the T5, T6, and T7 vertebral bodies." On further evaluation by an orthopaedic surgeon, the patient underwent a core biopsy of the involved T6 vertebral body. A positron emission tomograph-CT (PET-CT) showed hypermetabolic activity in the T6 area without other areas of disease, but the biopsy yielded inconclusive findings of non-specific fibrosis and crush artefact. The results of a repeat bone marrow biopsy performed 29 months from initial diagnosis were again consistent with CCyR and CMR. A PET-CT performed 3 months later showed no evidence of disease and stable diffuse sclerosis of the T6 vertebral body. The patient's back pain improved and he resumed his regular daily exercise.

Forty-two months from initial diagnosis of CML and 17 months from the onset of back pain, the patient developed acute worsening of back pain. An

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Table 1 Response milestones documented in our patient

	3 Months	6 Months	12 Months	25 Months	42 Months
CHR*	*	*	*	*	*
CCyR†			†	†	†
CMR‡			‡	‡	‡
GS§					§

*Complete haematological response.

†Complete cytogenetic response.

‡Complete molecular response.

§Granulocytic sarcoma.

MRI of the thoracic spine showed spinal canal stenosis at the level of T6 caused by a soft tissue mass. Emergent decompressive surgery was performed and the mass was resected. Pathological examination of the mass showed “a neoplastic population of medium sized cells that infiltrate through fat and fibrous tissue. The cells have irregular nuclei, fine chromatin, and small nucleoli. In the background are numerous mature appearing eosinophils admixed with a lesser amount of granulocytic precursors. Immunohistochemical stains were positive for CD45, CD43, CD117, and CD34. MPO and CD68 showed focal positivity. CD3, CD20, PAX5, and Oct-2 highlight background T and B-Cells. Tdt was negative.” The pathological findings were consistent with GS. FISH analysis on the tissue was positive for chromosomal translocation t(9;22)(q34;q11.2) in 94% of nuclei. A bone marrow biopsy was performed again and showed normocellular marrow and trilineage haematopoiesis with no evidence of CML or acute leukaemia. Cytogenetic and FISH analysis were again negative for evidence of relapsed CML. A repeat PET-CT revealed new areas of enhancement over the T6 vertebra and the left preauricular area. The patient underwent biopsy of the left preauricular lesion, which was negative for a neoplastic process on pathological examination.

OUTCOME AND FOLLOW-UP

The patient was subsequently referred to an outside facility for further management and treatment with plans to undergo a bone marrow transplant. He was given induction chemotherapy with cytarabine, daunorubicin, etoposide and ponatinib. The patient cleared his disease with this induction regimen as seen by a negative PET-CT. A myeloablative haploidentical transplant with busulfan/cyclophosphamide conditioning was then performed. The patient received an ABO compatible, cytomegalovirus negative, bone marrow transplant from his brother. The patient's post-transplant course was relatively unremarkable, however, he had refractory anaemia and thrombocytopenia

that was thought to be secondary to ponatinib therapy. As the patient did not have any mutational resistance to tyrosine kinase inhibitors, he was switched from ponatinib to dasatinib and has been tolerating it well. One-year post-transplant, remission has been maintained. The patient's bone marrow remains normocellular and PET-CT remains negative. The clinical and laboratory characteristics of this case are summarised in [table 1](#).

DISCUSSION

GS describes any solid tumour associated with acute leukaemia or MDS.¹ Our patient developed GS while in CCyR and MMR of his CML. It has been reported that certain cytogenetic abnormalities, such as t(8;21), are associated with a higher incidence of GS,⁵ but our patient did not have this abnormality. There have been case reports that describe the occurrence of GS in a number of rare scenarios: (1) isolated GS without the presence of bone marrow involvement preceding the development of AML^{4, 6}; (2) thoracic GS as the presenting manifestation of CML in blast crisis⁷ and (3) extramedullary blast crisis occurring after remission of CML treated with allogeneic stem cell transplantation (SCT).^{8, 9} We report an extremely rare case of GS occurring after CCyR is achieved with first-line imatinib for the treatment of chronic-phase CML. To the best of our knowledge, there are only three other cases of extramedullary blast crisis in the setting of CCyR achieved with imatinib therapy. Two of these cases were reported in an editorial written in response to Jabbour *et al*'s case series of sudden blastic transformation in CML treated with imatinib.^{10, 11} Matsuda *et al* described the third case: a 17-year-old male patient who developed leptomeningeal blast crisis after achieving CCyR with 4 months of imatinib therapy for chronic-phase CML. This patient then developed recurrent GS in the neck derived from a different clone after treatment of his initial blast crisis, again in the setting of CCyR of the bone marrow.¹² A comparative summary of the characteristics of the four patients is outlined in [table 2](#).

It is reasonable to hypothesise that our patient acquired an extramedullary, imatinib-resistant CML clone and remained with a cytogenetically negative bone marrow. This case poses a management dilemma because the patient's disease process cannot be well defined and is not typical of a CML ‘blast crisis’, which usually involves the bone marrow. Standard of care for a CML blast crisis includes use of a tyrosine kinase inhibitor, a multiagent induction regimen, involved radiotherapy to symptomatic areas of disease, central nervous system prophylaxis and allogeneic SCT.¹³ Allogeneic SCT is indicated, as isolated GS typically progresses to become systemic.¹ Studies by Pileri *et al* and Chevallier *et al* have demonstrated the superiority of SCT in patients with GS as compared with patients who did not

Table 2 GS in the setting of CCyR achieved with imatinib therapy

Cases	Our patient	Patient 1 ¹⁰	Patient 2 ¹⁰	Patient 3 ¹²
Age at diagnosis	30	62	54	17
CML phase at diagnosis	Chronic	Chronic	Chronic	Chronic
Months until CCyR	12 months	12 months	6 months on imatinib	4 months
Therapy	Imatinib 400 mg/day	Imatinib 600 mg/day	Interferon, then imatinib 400 mg/day	Imatinib 400 mg/day
Bone marrow status at EM blast crisis	MMR, CCyR	MMR, CCyR	CCyR	CCyR
Location of GS	Bone-spine	Small bowel, brain	Skin	CNS-leptomeningeal
Prior marrow blast crisis?	No	Yes	No	No
Time until EM blast crisis from initial diagnosis	42 months	62 months	30 months	4 months

CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; CNS, central nervous system; EM, extramedullary; GS, granulocytic sarcoma; MMR, major molecular response.

receive SCT.^{14–16} Overall survival and disease-free survival have been cited as high as 47% and 36% at 5 years, respectively. The best outcomes were seen in patients with GS who achieved complete remission via AML-induction such as chemotherapy followed by SCT.^{13 14}

We report this case to increase awareness that GS can occur in patients with CML despite documented CHR, CCyR and CMR, and the presentation can be extremely atypical, mimicking a variety of medical conditions.

Learning points

- ▶ Although rare, granulocytic sarcoma (GS) can occur in patients with chronic myeloid leukaemia (CML) despite documented complete haematological response, complete cytogenetic response and complete molecular response.
- ▶ It is important to remain vigilant in diagnosing cause of back pain and atypical symptoms in patients with a history of leukaemia.
- ▶ The use of stem cell transplantation should be considered in patients with GS, even in the setting of CML.

Competing interests None.

Patient consent Obtained.

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