Granulocytic sarcoma of the stomach: relapse after hematopoietic stem-cell transplantation for chronic myeloid leukemia

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Hematol Oncol Stem Cell Ther 2010; 3(2): 94-98

An 18-year-old male underwent an allogeneic hematopoietic stem cell transplantation (allo-HSCT) for chronic myeloid leukemia (CML) in the first late chronic phase. On day 132, he was readmitted to the hospital with nausea, vomiting and nodular lesions on endoscopy. A diagnosis of granulocytic sarcoma of the stomach was made. Bone marrow cytogenetic analysis for the Philadelphia chromosome and nested polymerase chain reaction for BCR-ABL1 were both negative. Immunosuppression was abruptly discontinued, and by day 180, all gastric lesions had completely disappeared. However, there were histological signs of graft-versus-host disease. The patient developed progressive anorexia and elevated hepatic enzymes, which prompted the reintroduction of cyclosporine. Considering the risk of another relapse, imatinib mesylate (IM) 600 mg/day was started. The patient’s condition improved, and there was no evidence of disease recurrence at 36 months after relapse. Relapse of CML is the commonest cause of treatment failure after allo-HSCT. On rare occasions, a localized extramedullary presentation is seen. Unless properly treated, other extramedullary relapse sites and/or marrow infiltration usually occur. Withdrawal of immunosuppression, along with IM therapy seems to be an acceptable approach in this setting.

Relapse of the underlying disease is the commonest cause of treatment failure after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and is related to a poorer outcome. Most relapses occur within the first two years of transplant. Chronic myeloid leukemia (CML) in chronic phase is among those with the lowest rates (10%-30%) of relapse. On rare occasions, an isolated extramedullary presentation is seen. In a large retrospective multicenter survey by Békassy et al, extramedullary relapse was reported in only 6 of 2753 (0.22%) grafted patients among the CML/myelodysplastic subgroup. In this report, we describe a rare presenting feature of post-transplant relapse of CML and discuss the main therapeutic alternatives in this setting.

CASE
An 18-year-old male underwent an allo-HSCT for CML in first late chronic phase in December 2006. He had been diagnosed with Philadelphia chromosome-positive (Ph+) CML in December 2003 and, since imatinib mesylate (IM) was not available as first-line treatment, interferon alpha (IFN-α) was used. Only a minor cytogenetic response was observed after more than two years of treatment. As an HLAtmatched unrelated male donor was available, an HSCT was performed. The conditioning regimen consisted of busulfan, cyclophosphamide and antithymocyte globulin. Cyclosporine and methotrexate were used for graft-versus-host disease (GVHD) prophylaxis. Engraftment occurred at day 30. On day 63, he presented with a grade I GVHD of the skin, which was treated with oral steroids. After two weeks, steroids were progressively tapered off. Three months after transplant, cytogenetic analysis for the Ph chromosome and nested polymerase chain reaction (PCR) for BCR-ABL1 were both negative. On day 132, he was readmitted to hospital due to a three-day history of vomiting and nausea. The physical examination was unremarkable. The complete blood count and chemistry profile
were normal. Presuming occurrence of gastric GVHD, upper gastrointestinal endoscopy was performed. The exam revealed four erythematous round nodules on the gastric mucosa, with elevated borders and diameters varying between 10 mm and 35 mm (Figure 1). Biopsies were performed and a histopathological/immunohistochemical examination showed a diffuse infiltrate of immature myeloid cells in the mucosa (Figure 2). Fluorescent in situ hybridization (FISH) analysis was positive for BCR-ABL1, consistent with a diagnosis of granulocytic sarcoma (Figure 3). Bone marrow aspirate and biopsy showed no evidence of leukemia. Cytogenetic analysis and nested PCR remained negative. There was no sign of active GVHD at that point, so immunosuppression was immediately stopped. After two weeks of drug discontinuation, a second endoscopy was performed. A significant regression of the two larger lesions and disappearance of the two smaller ones were observed. Given the response achieved, it was decided not to perform a donor lymphocyte infusion (DLI), and instead follow the remaining lesions with serial endoscopies. On day 180, complete disappearance of the nodules was observed. There were no signs of CML infiltration on histological evaluation, but signs of GVHD were present. The patient evolved with progressive anorexia and a significant increase in hepatic enzymes. Cyclosporine was reintroduced and, because of the risk of relapse, we decided to start with IM 600 mg/day. The patient’s condition improved, and subsequent endoscopies showed no evidence of disease recurrence at 36 months after relapse. No major drug toxicity was noted. He developed chronic limited GVHD of the skin, and cyclosporine was being tapered, but otherwise the patient was well. The patient was in ongoing complete molecular remission (as evidenced by real-time quantitative PCR negativity for BCR-ABL1 transcripts) at a follow-up of 36 months after relapse.

**DISCUSSION**

Granulocytic sarcoma, also known as myeloid sarcoma or chloroma, is a localized extramedullary tumor mass consisting of immature cells of granulocytic lineage in different maturation steps. When presenting as post-transplant relapse, it most often occurs before or concurrently with the onset of marrow infiltration. In the first case, a misdiagnosis of lymphoma is frequently made. In our patient, FISH analysis of the gastric mucosa lesions confirmed the CML origin of the infiltrating cells.

**Figure 1.** Upper gastrointestinal endoscopy showing erythematous round nodules with central ulceration and elevated borders, extending from the gastric fundus to the antrum-corpus transition zone (lesser curvature).

**Figure 2.** Granulocytic sarcoma in gastric mucosa. A) Low power field showing decreased glandular population and increased cellularity in the lamina propria on the right-hand side of the photograph; on the left-hand side, normal gastric mucosa (hematoxylin and eosin stain 50×). B) Higher magnification showing neoplastic infiltration of the lamina propria by immature cells of myeloid lineage, red arrows (hematoxylin and eosin stain 400×).
Detection of BCR-ABL1 transcripts by PCR has a prominent role in the early prediction of full-blown relapse of CML.\textsuperscript{7} In our case, PCR for BCR-ABL1 was negative at day 90 and was not capable of predicting overt disease, which was noticed less than two months later. This suggests a greater likelihood of isolated extramedullary relapse. We cannot rule out whether the patient had a gastric lesion prior to transplantation. The underlying disease may have remained subclinical until the post-transplant period, wherein an unfavorable immunological background may have contributed to the occurrence of overt disease.

Granulocytic sarcomas can involve virtually any organ.\textsuperscript{2,3} CML seems to have a tendency to relapse in bone, which in turn is associated with subsequent marrow relapse and short survival.\textsuperscript{7} Other organs, particularly the gastrointestinal tract, are much less frequently affected.\textsuperscript{2,3,8,9} A recent case series by Cunningham analyzed 35 first clinical extramedullary CML relapses after HSCT.\textsuperscript{7} In 24 of these cases, extramedullary sites were the first signs of relapse, at a median of 13 months post-HSCT, with or without simultaneous marrow relapse. There were only two reported patients with gastrointestinal relapse, both of whom died.\textsuperscript{8,9} Most cases were treated with radiotherapy, and only half received chemotherapy. None of the cases studied reported use of IM. Thirty of the 35 patients died within 12 months of relapse.

Treatment of extramedullary relapse in CML has generally not resulted in long survival.\textsuperscript{4} A single relapse site is usually followed, within months, by other extramedullary relapses and/or overt leukemia, unless prompt and aggressive treatment is undertaken.\textsuperscript{2,10} Post-transplant reports have varied in description of therapy details, and there does not seem to be a consensus as to the best therapeutic approach in this setting.\textsuperscript{2,3}

Surgery or radiotherapy alone may be effective in local disease control, but do not affect survival.\textsuperscript{10} Encouraging remission rates are seen with DLI.\textsuperscript{11} At present, this is the standard front-line approach for CML relapse after allografting, since it is capable of inducing long-term molecular remissions and restoring full donor chimerism.\textsuperscript{11} However, there is some evidence that granulocytic sarcomas exhibit a poorer response to chemotherapy and to the graft-versus-leukemia (GVL) effect, probably due to specific biologic properties of the leukemic cells at extramedullary sites, including increased tissue invasion and adhesion abilities.\textsuperscript{12} Cells exhibiting tumor growth may, therefore, require longer exposure to treatment for complete eradication. There are some reports of post-DLI extramedullary relapse in the presence of continuous marrow remission, which suggests an uneven medullary and extramedullary GVL effect.\textsuperscript{13} In a study by Chong et al, patients with extramedullary relapse of a variety of hematological malignancies appeared to respond to cytotoxic therapy but not to DLI.\textsuperscript{14} While patients with chronic GVHD have a lower overall relapse risk, they may be more prone to delayed relapse at extramedullary sites.\textsuperscript{14} Moreover, a study by Raiola et al showed a probability of DLI-related mortality of 44% for unrelated donor transplants as compared to a 9% rate for fully-matched siblings, mainly attributable to post-DLI GVHD.\textsuperscript{15} Relapse type was the major predictor of response: patients with accelerated phase or blast crisis exhibited a response rate of only 36% to DLI, as opposed to 100% in those in molecular relapse alone.

A simple strategy for treating post-transplant relapse of CML is discontinuing immunosuppressive GVHD prophylaxis so as to restore the GVL effect, but successes have been anecdotal in the literature.\textsuperscript{16} As mentioned in our report, considering the favorable response attained by the patient while withdrawing immunosuppression, as well as the side effects of DLI reported in the literature, particularly in the unrelated donor transplant setting, we decided to withhold this procedure.

The advent of IM, a tyrosine kinase inhibitor of BCR-ABL fusion-gene-positive cells, has revolutionized the treatment of CML, and has had some promising results in the post-transplant relapse scenario.\textsuperscript{17} However, the finding of granulocytic sarcoma lesions, as in the patient reported here, implies occurrence of relapse in blast crisis, wherein responses to IM tend to be of short duration. In a series of 128 patients with CML relapse after allografting, only 22% of those in...
blast crisis achieved a complete cytogenetic response with IM, and there were no complete molecular responses in this group.\textsuperscript{17}

In a recent retrospective study of 16 cases of post-transplant relapse of CML, the response rate to IM as front-line therapy at relapse, or as second- or third-line therapy after failure of DLI and/or IFN-\(\alpha\)-was as expected from treatment with DLI alone.\textsuperscript{18} Fifteen patients achieved cytogenetic and molecular responses (75\% obtained RT-PCR negativity), and the patient who had relapsed in blast crisis achieved ongoing complete molecular remission, after a follow-up of 45 months, with combined therapy of IM and DLI. In all of these cases, IM showed an acceptable side-effect profile, and no GVHD reaction was seen, nor did cases of prior GVHD worsen during treatment. Therefore, IM could be considered for first-line therapy when DLI is not available or if the worrisome side effects of this procedure are expected. In our case, the patient responded well to withdrawal of immunosuppression, as evidenced by serial endoscopies, and it seemed reasonable to keep him on maintenance therapy with IM (at a dose of 600 mg daily), since the risk of overt relapse was high.

In conclusion, a greater awareness of the possibility of post-HSCT extramedullary relapse of CML once suspicious symptoms or lesions are encountered, such as in our case, may allow early treatment of a potentially curable disease. Dose-adjustment or discontinuation of immunosuppression, along with IM therapy, seems to be an acceptable approach in this setting. A better understanding of the nature, prognosis, and treatment options of this rare condition may help patients achieve long-lasting remissions.

Acknowledgments
We are grateful to the whole transplant team for participation in patient assistance.

There are no conflicts of interest to declare.

Author contribution:
A.V.M. participated in acquisition of data and review of the literature, and drafted and revised the article; I.F.F. performed histopathological workup, and assisted in writing and revision of the article; F.M.O. performed cytogenetic analyses, and assisted in revision of the article; C.C.R. performed upper gastrointestinal endoscopy exams, and assisted in revision of the article; C.M.C.M also performed upper gastrointestinal endoscopy exams, and assisted in revision of the article; A.K.V. assisted in acquisition of data and revision of the article; L.P.F.C. performed immunohistochemical workup, and assisted in revision of the manuscript; E.M.R. participated in cytogenetic analysis and critical revision of the material; N.C.D.C. assisted in acquisition of data and critical revision of the article; H.B. participated in conception, drafting and critical revision of the article; all authors participated in final approval of the material for publishing.
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