Gelatinous Marrow Transformation in an Imatinib-Treated CML Patient with Pancytopenia Following Severe Sepsis

Pallavi Agrawal · Prashant Sharma ·
Vikram Narang · Neelam Varma ·
Pankaj Malhotra · Subhash Varma

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Dear Sir,

We read with interest the article by Srinivas et al. [1] describing morphological changes in bone marrows of chronic myeloid leukemia (CML) patients treated with imatinib mesylate (IM). We would like to share our experience with one such case with an unusual marrow finding.

A 60-year-old male, a chronic smoker, was first diagnosed with low-grade transitional cell carcinoma (TCC), urinary bladder in 2003 after he underwent endoscopic transurethral resection of a bladder tumor (TURBT). He suffered local recurrences in 2004 and 2005, and repeat TURBTs were done followed by administration of intravesical BCG, and subsequently gemcitabine and mitomycin. The third TURBT in 2005 was complicated by bladder perforation requiring laparotomic repair.

He remained well till 2008 when routine follow-up hemograms revealed persistent leukocytosis. The spleen, impalpable clinically, was mildly enlarged on ultrasound. Investigations revealed hemoglobin 8.8 gm %, platelets $868 \times 10^9/l$ and TLC $68.3 \times 10^9/l$ with 56 % neutrophils, 2 % lymphocytes, 5 % eosinophils, 10 % basophils, 1 % promyelocytes, 13 % myelocytes and 13 % metamyelocytes. Leukocyte alkaline phosphatase score was five (reference range 40–100) and reverse transcriptase PCR for the p210 bcr-abl fusion transcript was positive. He was thus diagnosed as CML in chronic phase and started on IM 400 mg OD. Complete hematological

response (CHR) was subsequently documented at 2 months and complete cytogenetic response at 2 years of therapy.

In August 2011, while in CHR, his TCC bladder recurred, now extending into the right ureter causing right hydronephrosis. A radical cystectomy with a right nephrectomy and left ureteric ileal conduit was done. Three months post-operatively, he developed productive cough and hemoptysis requiring hospitalization. He was found to have bilateral (right > left) lobar pneumonia and deteriorated rapidly into generalized sepsis and disseminated intravascular coagulation complicated by acute renal failure. Urine culture grew *Klebsiella pneumoniae* sensitive to gentamicin, tobramycin and nitrofurantoin. He was treated in the medical intensive care unit and after appropriate antibiotic and supportive therapy, improved clinically over 1 month. However, even post clinical recovery he continued to have pancytopenia with Hb 7–8 gm %, TLC $2-3 \times 10^9/l$ and platelets $80-100 \times 10^9/l$. A bone marrow aspiration performed in February 2012 revealed particulate and cellular marrow with cells of all hemopoietic lineages. Strikingly, there was extensive deposition of extracellular pink fibrillary gelatinous material that was positive for Alcian blue stain at pH 2.5 (Fig. 1) and negative for periodic acid Schiff. A diagnosis of gelatinous marrow transformation was made. He continues to be on follow-up with persistent leucopenia and mild thrombocytopenia 4 months later while still on IM.

Gelatinous marrow transformation (GMT) is classically characterized by replacement of normal hematopoietic tissue and adipocytes of the marrow by amorphous gelatin-like extracellular matrix consisting of hyaluronic acid [2–4]. It has been reported in many conditions including anorexia nervosa and cachexia of chronic debilitating conditions like severe malnutrition, AIDS, acute leukemias and lymphoma (especially post-chemotherapy) and infections like tuberculosis and kala-azar [2–4].

P. Agrawal · P. Sharma (✉) · V. Narang · N. Varma
Department of Haematology, Postgraduate Institute of Medical
Education and Research, Sector 12, Chandigarh, India
e-mail: sharma.prashant@pgimer.edu.in

P. Malhotra · S. Varma
Department of Internal Medicine, Postgraduate Institute
of Medical Education and Research, Chandigarh, India

Fig. 1 Cellular bone marrow shows hemopoietic elements of all lineages entrapped in eosinophilic fibrillary gelatin-like material (MGG-Giemsa, $\times 400$). The panel on the *lower right* shows the alcianphilic extracellular material (Alcian blue at pH 2.5, eosin counterstain, $\times 400$)

Table 1 A summary of previously reported cases of gelatinous marrow transformation in CML on imatinib mesylate therapy

S. No	Reference	Age/Gender	Associated cytopenias	Duration since diagnosis or initiation of treatment to detection of GMT	Associated co-morbidities
1.	Ram et al. [5]	53 year, male	Anemia, leukopenia	1 year after initiation of IM	Nil mentioned
2.	Ram et al. [5]	23 year, female	Nil	22 months after diagnosis	Nil mentioned
3.	Hong et al. [7]	44 year, male	Nil	11 months after diagnosis	Nil mentioned
4.	Paul et al. [8]	Not mentioned (one case as part of larger series)	Not specified	Not mentioned	Nil mentioned
5.	Thukral et al. [6]	67 year, male	Pancytopenia	Not mentioned	Nil mentioned
6.	Current case	60 year, male	Pancytopenia	32 months after diagnosis of CML	Recurrent TCC bladder, history of chemotherapy, uretero-ileal anastomosis, sepsis–DIC–renal failure

IM Imatinib mesylate, TCC transitional cell carcinoma, DIC disseminated intravascular coagulation

GMT occurring in imatinib-treated CML is a relatively recently described phenomenon [5–8]. The precise mechanism remains obscure although drug-induced down-regulation of transforming growth factor beta signal transduction resulting in reduced synthesis of normal extracellular matrix (ECM) as well as blockade of platelet derived growth

factor receptor-mediated fibrosis have been implicated [5, 6]. Only two of the five previously reported cases of GMT (summarized in Table 1) in association with CML had pancytopenia, one had bicytopenia and two had normal blood counts at the time of diagnosis of GMT [5–8]. None of the previous authors reported any co-morbidities unlike our

patient who had recently emerged from a serious systemic infection and had a history of recurring visceral malignancy treated with chemotherapy. Our case also had the longest lag period between initiation of therapy and development of GMT (Table 1). In this light his GMT appears unlikely to be attributable to IM or to CML, and was possibly multifactorial in origin with a major contribution by the genitourinary-origin sepsis.

Morphologically, the presence of Alcian blue positivity at pH 2.5 confirmed the hyaluronic acid nature and excluded marrow edema while PAS negativity made it unlikely that the material present was normal extracellular matrix or ground substance. A variant of GMT without fat cell atrophy has also been described in acute myeloblastic leukemia after chemotherapy [9]. This pattern was also seen in a case of CML described by Hong et al. [7] and possibly our patient too has this variant.

In conclusion, this case represents, to the best of our knowledge, only the sixth reported occurrence of GMT in IM-treated CML. Whether it was an incidental finding consequent to the recent infection or, less likely but as in other reported cases, a reflection of disease activity or a drug adverse event remains open to conjecture. However, it does illustrate the hematologist's commonly faced clinical dilemma of correlating abnormal blood pictures (in this case, pancytopenia) with unusual pathology findings (GMT) and establishing causality in the patient with multiple co-morbid conditions.

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