Herpes zoster complicating imatinib mesylate for gastrointestinal stromal tumour
Durosinmi MA, Ogbe PO, Salawu L, Oyekunle AA

ABSTRACT
Varicella zoster virus (VZV) infection is uncommon in patients with gastrointestinal stromal tumour (GIST) and who have not been exposed to extensive radiotherapy and/or high-dose chemotherapy. We report a 56-year-old Nigerian man with GIST who developed VZV infection while on imatinib mesylate therapy. From August 2003 to November 2005, 64 patients (GIST/CML = 6/58) were enrolled into an ongoing Glivec (imatinib mesylate) international patient-assistance programme therapy for Philadelphia/bcr-abl-positive chronic myeloid leukaemia (CML) and CD117-positive GIST patients at Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria. The patient developed herpes zoster (HZ) infection 23 months into therapy with Glivec. With his absolute lymphocyte count at 2,774 cells per microlitre and CD4 count at 950 cells per microlitre, no obvious immunological defect was observed. Prompt resolution of symptoms without sequelae was achieved by treating with acyclovir, analgesic and dressing of lesions with desiccant. To our knowledge, this is the first reported case of HZ infection in a patient with GIST on Glivec therapy, and the response is similar to that of CML patients who developed VZV while on similar therapy.

Keywords: gastrointestinal stromal tumour, herpes zoster, imatinib mesylate, varicella zoster virus

INTRODUCTION
Gastrointestinal stromal tumour (GIST) is currently defined as a c-kit/CD117-positive mesenchymal tumour with specific histological characteristics occurring in the gastrointestinal tract(13). Historically, GISTs were classified as either benign or malignant, with the majority diagnosed as benign. Recent evidence however suggests that all GISTs have at least some malignant potential(9). Although over 80% of sporadic cases of GISTs are associated with c-kit mutation, and other mutations occur in the KIT-related kinase gene PDGF receptor alpha in about 8% of others(49), the neurofibromatosis type 1 (NF1)-related gastrointestinal stromal tumour lacks either of these characteristic activating oncogenes(50). The pathogenetic basis of GIST in NF1 is believed to arise from a somatic inactivation of the wild-type NF1 allele in the tumour, resulting in inactivation of neurofibromin (the protein encoded by NF1) and oncogenic transformation of the tissue(51). Several cases of the so-called extra-gastrointestinal stromal tumours have also been reported(16-18).

Cutaneous reactions of varying severity have been reported in association with some of the biotherapies including monoclonal antibodies, soluble cytokines and tyrosine kinase inhibitors currently in use in medicine(54). Skin reactions are particularly common in Glivec® (imatinib mesylate) therapy, and the risk is dose-related, suggesting that the complications result from pharmacological effect, rather than true hypersensitivity reactions(10-13,19). The incidence of imatinib-associated skin reactions varies from 9.5% to 69%(14,18). In a number of review articles and original publications, including the phase 1 reports of imatinib in chronic myeloid leukaemia (CML)(19) and in GIST(19), the documented cases of imatinib-related cutaneous reactions include self-limiting dermatitic rashes, maculopapular eruptions, erythematous eruptions, skin desquamation and periorbital oedema. Rarer skin reactions in imatinib mesylate therapy include hypopigmentation, lichenoid reactions, pityriasiform eruptions, pityriasis rosea, psoriasis, reactivation or induction of porphyria cutanea tarda, as well as neutrophilic eccrine hidradenitis(14,17,18).

The majority of the imatinib-related skin reactions resolve with administration of oral or topical corticosteroids(18). The generalised hypopigmentation seen in Glivec® therapy is dose-related and is usually reversible, with cessation of therapy or dose reduction(14,18,19). Occasionally, more serious cutaneous lesions necessitating imatinib withdrawal have been reported such as graft-versus-host-like drug reaction, erythema nodosum and small vessel vasculitis(20), acute generalised exanthematous pustulosis(20-22), and Stevens-Johnson syndrome(23). Clark et al reported mycosis
fungoides-like dermatitis, comprising predominantly CD3+ cells in a patient with GIST treated with imatinib mesylate.

Herpes zoster (HZ) due to Varicella zoster virus infection is an uncommon cutaneous complication of imatinib mesylate therapy. HZ can be very severe in the immunocompromised host, compared to immunocompetent individuals. Formation of lesions may continue for up to two weeks, and healing may not occur until three to four weeks later. Herpes zoster occurs rarely in immunocompetent persons, but immunocompromised individuals are at greater risk, in particular leukaemia and lymphoma patients, individuals undergoing stem cell transplantation, patients on chronic immunosuppressive therapy, or those with exposure to radiation and post-splenectomy patients. Patients with dysfunctional cell-mediated immune systems are particularly at risk for cutaneous dissemination and visceral involvement, including pneumonitis, hepatitis, and meningoencephalitis. However, it is rarely fatal. To our knowledge, this is the first report of HZ in a patient with GIST on imatinib mesylate therapy. A similar report in 16 patients with CML on imatinib mesylate was recently published.

**CASE REPORT**

A 56-year-old male civil servant presented with a history of sudden-onset of dysphagia without odynophagia or significant weight loss. He was placed on antibiotics, with a presumptive diagnosis of bacterial pharyngitis without improvement. An upper gastrointestinal endoscopic biopsy raised the possibility of a malignancy. Computed tomography and positron emission tomography of the abdomen (done in London) confirmed a gastric growth which was biopsied by ultrasonographically-guided laparoscopy. The liver, spleen and kidneys were free of focal lesion. Immunocytochemistry of the tumour cell confirmed CD117-positive GIST, and he was commenced on imatinib mesylate 400 mg daily in November 2003.

In October 2005, after about two years of imatinib mesylate therapy, he developed multiple, painful and exquisitely tender blisters, with a distinctly dermatomal distribution over the left side of the trunk (Fig. 1). Serial neutrophil and lymphocyte counts are shown in Fig. 2. CD4 count at the time of eruption was 950 cells/µL. A clinical diagnosis of reactivated HZ was made, and he was commenced on Acyclovir, with significant prompt alleviation of symptoms within one week.

**DISCUSSION**

Bizarre presentations of GIST are not uncommon in clinical practice. However, it rarely presents with de novo immunosuppression, a situation more commonly seen in another subgroup of patients who have undergone radiotherapy and/or intensive chemotherapy. In the case under discussion, the patient commenced imatinib mesylate from the outset without any surgical, chemo- or radio-therapeutic pre-treatment. He had also not been on any medication with immunosuppressive actions. Furthermore, all of patient’s lymphocyte counts (Fig. 2) and the CD4 counts at the time of infection were well within normal limits. The dermatomal presentation of a vesicular rash with severe pain is classical of HZ infection. There was also no evidence to suggest a nosocomial infection.

Considering that the absolute lymphocyte (and CD4) counts were adequate, a functional defect in cell-mediated immune mechanisms can be the only plausible explanation for this presentation. As imatinib mesylate is a new drug, it is difficult to find convincing evidence of its immune effects. A selective
depletion of VZV-specific mature lymphocytes is theoretically possible, although the absence of evidence to suggest specific binding of imatinib to such a clone makes it statistically improbable. The HZ in this patient probably resulted from reactivation of dormant VZV infection due to impaired cell-mediated immunity and probably suppression of CD4 cell count in patients on long-term imatinib mesylate therapy.

The use of orally-administered acyclovir, valaciclovir or famciclovir has been associated with accelerated healing of lesions and resolution of zoster-associated pain in the immunocompetent adult. Acyclovir use in this patient may have contributed to early resolution of symptoms, without complications (e.g. infection, neuralgia, hepatitis, encephalitis). As we have yet to accumulate enough patients in our trial, it is still too early to comment on the possible frequency of HZ infection, but the cumulative incidence of this one case in all patients receiving imatinib mesylate is 1.6%.

We conclude that reactivation of latent herpes infections is a rare possibility in patients with GIST on imatinib mesylate therapy. The infection responds to antiviral therapy and it is quite possible that imatinib mesylate may interfere with cell-mediated immunity. It is however clear that only longer follow-up and a more detailed immunological analysis of a larger pool of patients with GIST on imatinib therapy can answer the many questions that this observation has raised.

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