CASE REPORT

Lymphomatoid granulomatosis in a patient previously diagnosed with a gastrointestinal stromal tumour and treated with imatinib

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A 39-year-old man with a history of recurrent malignant gastrointestinal stromal tumour (GIST) of the small bowel, treated with imatinib, presented with a 2-week history of shortness of breath, fluctuating fever, pancytopenia and bilateral airspace opacities. He was treated for pneumonia, but his condition deteriorated and he died 6 weeks after admission. We present the subsequent postmortem examination findings.

CLINICAL HISTORY

This is the case of a 39-year-old man, with a medical history of malignant gastrointestinal stromal tumour (GIST) of the small bowel, resected 2.5 years before this episode. Local recurrence and liver metastases occurred 18 months from initial diagnosis. Imatinib mesylate 400 mg once daily (Glivec; Novartis, Basel, Switzerland) was started, with a good clinical response (including a reduction in tumour size). Family history included a sister diagnosed with cancer and mother with a brain tumour (unfortunately, further information could not be obtained).

The patient was admitted in September 2004 with a 2-week history of gradually increasing shortness of breath, productive cough, fever and pleuritic chest pain, 12 months after imatinib was started. A chest x ray showed bilateral airspace opacities and a right pleural effusion (fig 1). Investigations showed a white cell count of 2.5×10^9 cells/l with lymphopenia (0.2×10^9 cells/l). No infective agents were identified. The patient was HIV-negative. Repeated antibiotic and antifungal treatment ultimately failed. Imatinib was stopped 10 days after admission without improvement in the clinical condition. However, after 10 days, there was gradual recovery of lymphopenia (fig 2).

The patient's condition continued to deteriorate and he died on the 43rd day of admission.

POSTMORTEM EXAMINATION FINDINGS

A consented limited, hospital postmortem examination of the heart and lungs was performed, which showed bilateral pleural effusions and partial or well-defined pale grey/tan nodules of variable size showing central necrosis and focal cavitation (fig 3). Lesions were present in all lobes of the right and left lungs, the largest measuring 14 cm. The heart was macroscopically normal.

HISTOLOGICAL FINDINGS

The lung showed no evidence of a metastatic GIST, and no CD117+ cell was present. However, the nodules showed large areas of necrosis, and viable tissue showed an angiocentric distribution of large CD20+ atypical lymphoid cells, and CD3+ small lymphocytes. These are the typical histological appearances of lymphomatoid granulomatosis (LYG), grade III (fig 4). Atypical cells were shown to contain Epstein–Barr virus (EBV; latent membrane protein and EBV-encoded RNA positivity).

Review of the original small bowel lesion confirmed the diagnosis of malignant spindle cell-type GIST. The tumour measured 11.5 cm. High mitotic count (>15 per high-power field), foci of necrosis, haemorrhage and a strongly positive immunohistochemical reaction with antibody CD117 were noted.

DISCUSSION

We report on the first documented patient to be diagnosed with two rare malignant lesions of different origin, GIST and LYG. These two lesions occurred at a young age. LYG presented 2.5 years after the initial diagnosis of GIST, and 12 months after imatinib treatment was commenced.

GIST is regarded as the most common mesenchymal tumour in the gastrointestinal tract, but it remains a rare tumour. These tumour cells show differentiation to interstitial cells of Cajal and are usually positive with the CD117 (KIT) marker.¹

About 20–30% of tumours arise in the small bowel.¹ Age distribution shows that it rarely occurs before the sixth decade, although cases have been reported in children.¹ Most GISTs are sporadic.¹ A few families with multiple GISTs have been reported, some of these related to a germline mutation in the KIT and PDGRA genes.^{2,3} Members of these families are not at great risk for any other malignancies.^{2,3} However, individuals with neurofibromatosis type 1 have been shown to be at increased risk of developing GISTs.⁴

Unresectable and recurrent or metastatic tumours can benefit from imatinib, a receptor tyrosine kinase inhibitor treatment, if the lesion has been shown to express c-KIT protein.⁵ The most commonly reported side effects are oedema, fatigue, skin changes and, more seriously, gastrointestinal haemorrhage (<http://www.pharma.us.novartis.com-gleevec-tabs.pdf>). Haematological toxicity such as neutropenia and hepatotoxicity are less commonly reported than in patients with chronic myelogenous leukaemia (<http://www.pharma.us.novartis.com-gleevec-tabs.pdf>). Some cases of interstitial pneumonitis have been recently reported.⁶ However, no case of secondary malignancy has been described.

LYG, recently defined as an extranodal lymphoproliferative disease of uncertain malignant potential, is a spectrum of rare angiocentric lymphoproliferative disorders.⁷ At its most severe, grade III may be regarded as a subset of B cell high-grade lymphoma, with angiodestruction, extensive necrosis and atypical cells dispersed among an abundant T cell reactive population.^{8–10} Most cases have been shown to be EBV related.^{9–11} The aetiology of LYG is uncertain, but an association with some T cell-mediated immune response deficiency has been suggested.^{8–11} Three grades have been described, consisting of a

Abbreviations: EBV, Epstein–Barr virus; GIST, gastrointestinal stromal tumour; LYG, lymphomatoid granulomatosis

Figure 1 Chest x ray (A) and computed tomography imaging (B) showing bilateral airspace opacities and right pleural effusion.

polymorphous cellular infiltrate showing variable numbers of large, atypical cells.⁸⁻¹² Grade I is difficult to diagnose on histological examination, as only scattered tumour cells are present, dispersed in an abundant population of non-atypical T cells.¹¹⁻¹² The main differential diagnosis at this stage is vasculitis. Grade III lesions morphologically resemble high-grade malignant lymphoid neoplasms.¹¹⁻¹²

This lymphoproliferative disorder is aggressive and difficult to diagnose; many of the reported cases have been diagnosed after death.⁹⁻¹² Clinical presentation is that of fatigue, fever and weight loss, together with respiratory symptoms.¹⁰⁻¹² LYG predominantly affects the lungs, and may involve other sites including the skin, gastrointestinal tract, kidneys and nervous system, and lymph nodes less commonly.⁸⁻¹¹⁻¹²

Investigations show bilateral multiple nodular masses that seem to coalesce or cavitate on chest x ray, which may be difficult to distinguish from infective causes.¹² Prognosis is usually poor.¹⁰⁻¹² The pathological findings are nodules of grey tissue in the lungs showing necrosis and cavitation due to angiodestructive features,⁸⁻¹⁰⁻¹² with the histological appearances described earlier.

The concurrence of these two rare lesions has not been previously reported, and could not show any causal relationship between both. The fact that they both occurred at a young age and the presence of a family history of cancer suggests that there may be a predisposing inherited factor. This does not correspond to any known syndrome.

Figure 2 Recovery of lymphocyte count. Imatinib mesylate treatment during hospital admission is indicated by black bar. The figure shows a marked improvement in the white cell count 10 days after discontinuation of imatinib.

LYG has been reported in patients with lymphopenia and T cell-mediated response deficiency,⁸⁻¹¹ but no such abnormality has ever been reported in patients with GIST. Furthermore, patients with familial GIST are not known to develop lymphomas,²⁻³ although there have been recent case reports of GIST occurring synchronously with gastric mucosa-associated lymphomas.¹³⁻¹⁴

However, imatinib is documented to cause severe lymphopenia (<http://www.pharma.us.novartis.com-gleevec-tabs.pdf>), as noted in this patient, who had received over 12 months of treatment, and LYG occurred while he was receiving long-standing imatinib treatment. It is interesting to note that lymphopenia improved after discontinuation of imatinib treatment. Several studies have shown the link between EBV and LYG, suggesting a role in its pathogenesis.¹¹ Latent viral proteins (latent membrane protein 1 and EBV nuclear antigen 2) have been identified in post-transplantation and HIV-related lymphoproliferative diseases.¹¹⁻¹⁵⁻¹⁶ LYG has been reported in cases of post-transplant immunodeficiency, HIV and immunosuppressive treatment.¹⁵⁻¹⁶ Whether imatinib-induced immunosuppression favoured the development of LYG should be considered, particularly in the context of a potential inherited immune response deficiency. Furthermore, there are no known studies showing direct involvement of imatinib in human carcinogenesis; however, early studies of the rat urogenital tract showed the occurrence of adenoma/carcinoma, and evaluation of other organs is ongoing (<http://www.pharma.us.novartis.com-gleevec-tabs.pdf>).

In conclusion, this case illustrates that LYG is difficult to diagnose clinically. It can mimic an infective process. One should keep this in mind as a possible diagnosis for antibiotic-resistant pneumonitis, with characteristic radiological features¹² especially in patients with spontaneous or drug-induced long-standing lymphopenia.

Figure 3 Lung with multiple soft whitish nodules with focal necrosis.

Figure 4 (A,B). Haematoxylin and eosin stains of lung lesions showing extensive necrosis containing large atypical cells with angiocentric distribution. (C,D). CD20 and latent membrane protein immunostaining showing positive large atypical cells.

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