Respiratory distress and sudden death of a patient with GSDIb chronic neutropenia: possible role of pegfilgrastim

The advent of commercial G-CSF preparations has considerably improved the survival and quality of life of patients with chronic neutropenia,[1] including patients with glycogenosis Ib.[2] Pegylated G-CSF was authorized in the early 2000s for chemotherapy-induced neutropenia,[3] allowing longer dosing intervals of what is often a chronic treatment. However, the kinetics of this drug have not been studied in patients with chronic neutropenia. We report a case that raises questions as to the safety of this drug in this setting.

The patient was diagnosed with glycogenosis Ib at birth, in 1976, based on biochemical findings with genetic confirmation. She developed severe neutropenia early in life, making her very susceptible to bacterial gum and gut infections. She also had multiple gastrointestinal complications such as chronic enteritis, and a Crohn-like radiological aspect, necessitating several operations (segmental colectomy in October 1990, discharge ileostomy in 1991, cecal resection in 1993). Following coloscopy in June 2002 she developed peritonitis requiring colonic resection, followed by total colectomy in July 2005.

Other complications linked to glycogenosis Ib included fluctuating hepatic adenomas first detected in 1987.

In 1995 she was treated with surgery alone for a polar malignancy of the right kidney.[4] At the same time she developed renal impairment with intermittent proteinuria (interstitial nephropathy) that subsequently remained stable.

In June 2002, after coloscopy, she had an episode of respiratory distress with white lung, leading to the diagnosis of pulmonary arterial hypertension (PAH). After the acute episode the PAH remained stable on diuretic treatment. This complication had already been reported in glycogenosis Ia.[5] She had severe hematologic disorders, including neutropenia, anemia and intermittent thrombocytopenia. Chronic G-CSF therapy was started

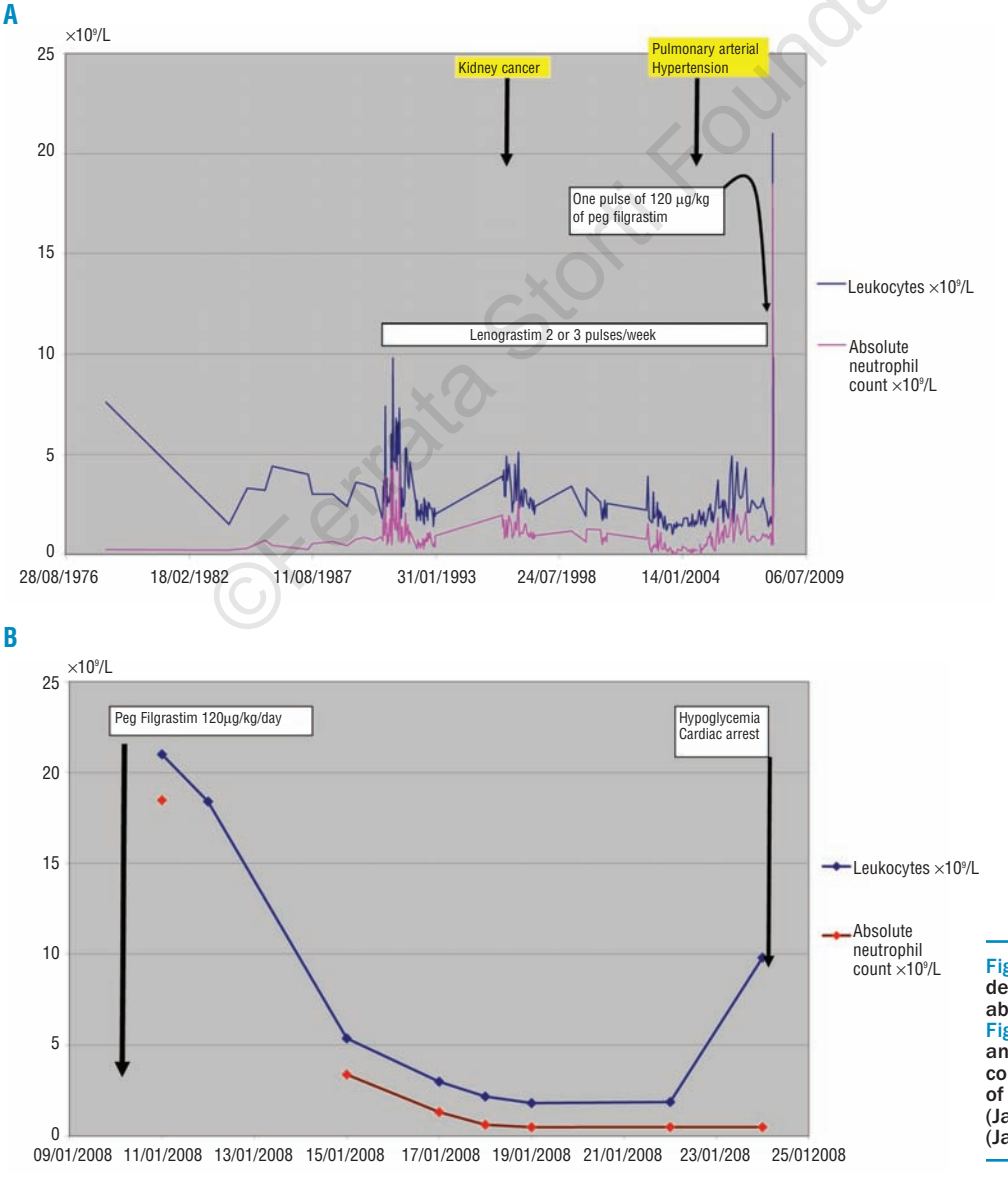
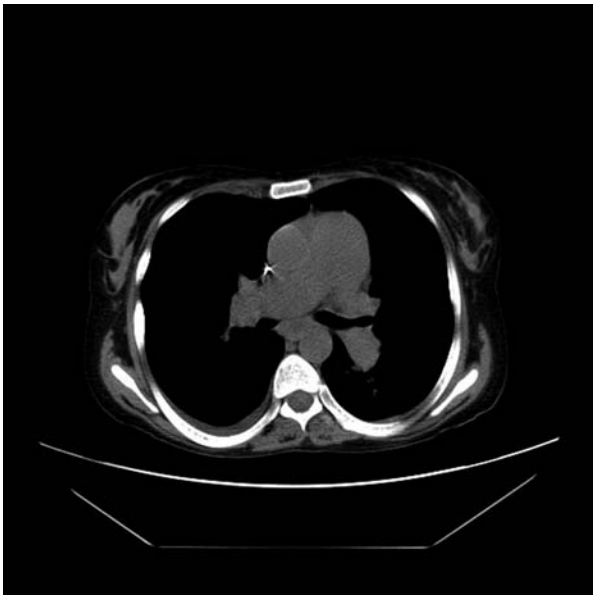
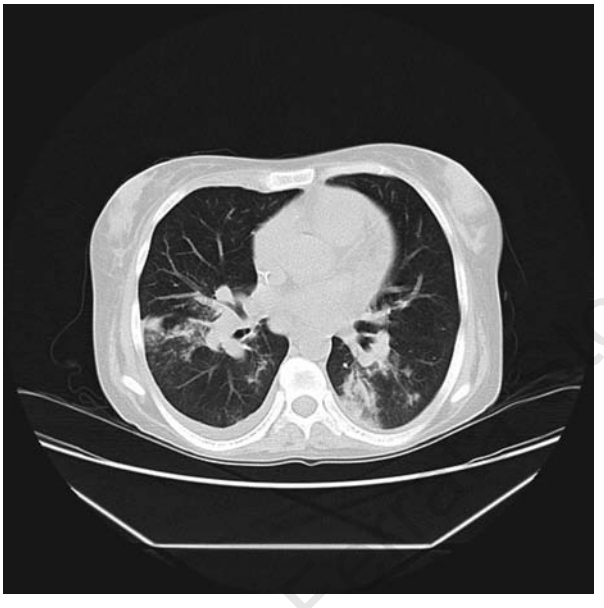


Figure 1A and B. Figure 1A depicts the patient's lifetime absolute neutrophil counts. Figure 1B depicts leukocyte and absolute neutrophil counts between the injection of 120 µg/kg peg filgrastim (Jan 10th, 2008) and death (Jan 25th, 2008).





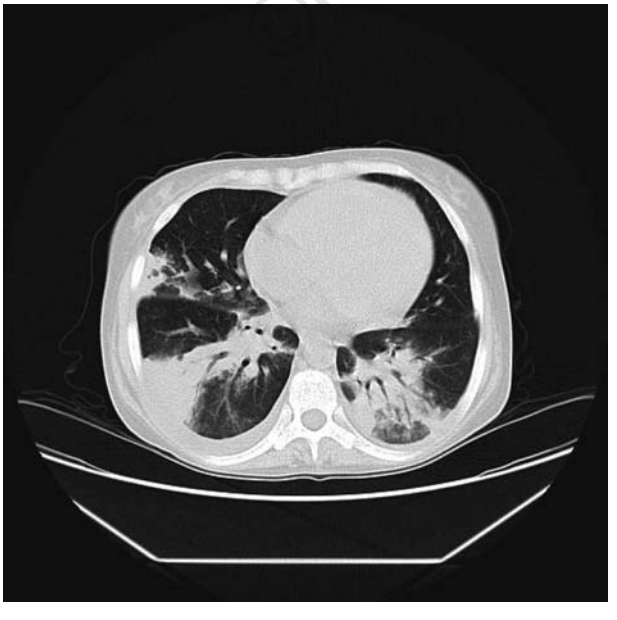


Figure 2 (left). Unenhanced CT scan obtained three days after pegfilgrastim administration, demonstrating marked enlargement of the main and right pulmonary arteries. The main pulmonary artery to aortic diameter ratio is greater than one. The maximal diameter of the pulmonary trunk is 42 mm.

in February 1991. Up to early January 2008 she received a total dose of 7,997 µg/kg. The mean dose per injection was 4.5 µg/kg and the mean interval between injections was three days (mean body weight 50 kg between 2006 and 2008). The drug used between February 1991 and 7th January 2008 was lenograstim. The leukocyte and neutrophils cell kinetics are shown in Figure 1A and B. No leukemic transformation was noted on the last bone marrow smear in November 2007. The anemia was treated with transfusions and erythropoietin.

In mid-December 2007 she was hospitalized with abdominal pain, bronchial congestion and severe anemia (6 g/dL). After transfusions and antibiotic therapy, she was discharged on 20th December and pegylated filgrastim was prescribed instead of lenograstim. The first injection of pegylated filgrastim took place on Thursday, 10th January 2008 and consisted of one 6,000-µg vial (120 µg/kg). On Friday 11th January she was hospitalized with respiratory distress at rest and on effort. She had signs of bronchitis and a body temperature of 37.9°C. The oxygen saturation was 94%. The white cell count was 21×10^9/L (19.4×10^9/L neutrophils), the hemoglobin 7.9 g/dL and the platelet count 268×10^9/L. The creatinemia was 215 µmol (normal value ~90) and the CRP was 122 mg/L. She also had metabolic acidosis. Chest radiography showed interstitial overload but no focal abnormalities. The ECG showed negative anteroapical T waves. Antibiotic therapy and fluid support were started, and a pack of red cells was transfused. Thoracic CT on 15th January showed marked enlargement of the main and right pulmonary arteries, with a main pulmonary artery to aortic diameter ratio greater than one, corresponding to pulmonary arterial hypertension (Figure 2), as well as symmetrical disseminated alveolar condensations, predominating at the lung bases. She was admitted to the intensive care unit on 12th January and returned to the general ward on 14th January. Her respiratory status improved but she had metabolic disorders and unstable glycemia. On 25th January she had generalized seizures (likely related to hypoglycemia), followed by refractory cardiorespiratory arrest and death.

This adverse event occurred just after an injection of pegylated filgrastim but might have been coincidental. Indeed, the patient developed pneumonia while neutropenic and was in poor general condition, with multiorgan failure and PAH. In this case, her death would have been due to metabolic failure related to her underlying disease.

However, it is also conceivable that pegylated filgrastim injection led both to an acute aggravation of PAH and to pulmonary vascular lesions culminating in death. Indeed, pegylated filgrastim releases a large amount of GCSF and leads to a very large increase in the number of circulating neutrophils, which are also activated.[6] The aggravation of PAH could be explained by pulmonary artery insult (due to neutrophils priming as already observed with filgrastim), followed by massive influx of neutrophils into the interstitium and pulmonary alveolae,[7] thus explaining the alveolar condensations observed on D5 of pegylated filgrastim therapy. The

cardiac arrest during an episode of hypoglycemia would, in this case, be due to the PAH aggravation after pegylated filgrastim injection. The lesions of the pulmonary arterioles would have worsened, thus explaining the gravity of the hypoglycemic seizures secondary to her metabolic disorders.

The sequence of events, together with the unusually severe hyperleukocytosis (her highest lifetime white cell count) in this neutropenic patient after pegylated G-CSF injection, as well as the absence of fever, and the known priming role of G-CSF for PMN, argue for a role of peg filgrastim in the onset of the respiratory distress. In contrast, the rise in CRP, together with the signs of bronchitis before pegylated G-CSF injection, support the first hypothesis.

This case must be considered in the light of the known adverse effect profile of pegylated G-CSF. Indeed, there are already several reports of severe adverse effects, including cases resembling that described here. A patient receiving chronic G-CSF therapy developed marked hyperleukocytosis and Sweet vascularitis after a single injection of pegylated filgrastim.[8] Pegylated filgrastim withdrawal led to an improvement three weeks after the last injection. In 2 other cases a neutrophil excess was associated with pyoderma gangrenosum[9] and lung disease,[10] with radiological characteristics similar to those found in our patient.

In conclusion, even if the link between pegylated filgrastim and our patient's respiratory distress cannot be proved, this drug should only be used with care in patients with pulmonary arterial hypertension, even when stable.

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Longitudinal growth retardation in a prepuberal girl with chronic myeloid leukemia on long-term treatment with imatinib

Recently Jonsson *et al.* reported on increased cortical bone mineralization as a side effect in imatinib treated adult patients with chronic myelogenous leukemia (CML).[1] Also for pediatric CML targeted therapy by this tyrosine kinase inhibitor has been replacing stem cell transplantation (SCT) as front-line treatment.[2] Thus, although CML is rare in childhood, the number of children treated by imatinib is constantly growing. However, side effects of imatinib on the immature skeleton might differ from adults. We here report on massive growth retardation while on imatinib treatment.

The patient was born as one of triplets at the 34th week of gestation (weight: 2540 g; length: 47 cm). Her further development was uneventful until the age of 5$_{1/2}$ years when Philadelphia$^+$ CML was diagnosed. Treatment with imatinib (Glivec™) starting in October 2005 was tolerated without specific side effects. Regular follow-up examinations confirmed ongoing remission and at 40 months on treatment the BCR-ABL rearrangement was undetectable. However, growth retardation had been observed already six months after treatment with imatinib had been initiated. While at diagnosis her body height was equivalent to the 74th percentile it fell to the 9th percentile after three years of treatment (Figure 1). Regular monitoring of bone biochemical markers exhibited increased excretion of urinary Ca, pyridinoline (PYR) and desoxypyridinoline (DPYR), reduced serum N-terminal propeptide of type I collagen (PINP) and increased serum osteocalcin (Table 1). X-ray of the left hand demonstrated skeletal age retardation of 22 months at the age of eight years. Further diagnostics showed partial growth hormone (GH) deficiency (IGF1: 43 ng/mL and 60 ng/mL at the age of seven years and eight years, respectively: normal values: 64-345 ng/mL). No other drugs beside imatinib had been taken by the patient. The two heterozygous triplet siblings showed normal hematologic parameters and their growth followed the 82nd and 55th percentiles, respectively.

Also in children, rapid control of Philadelphia$^+$ CML