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

Table 1. Analysis of biochemical markers of bone metabolism. (N) depicts normal values while pathological values are indicated by (↑) if increased, and by (↓) if decreased.

Specimen	Marker [unit]	Normal range	Age [years] Time on imatinib [weeks] 7 72	7 1/4 85	7 1/2 99	8 120	8 1/4 135	8 1/2 148
Plasma	PTH [µg/L]	11-43	27 (N)	22 (N)	27 (N)	30 (N)	52 (N)	30 (N)
	Osteocalcin [µg/L]	16-37	45 (↑)	44 (↑)	48 (↑)	37 (N)	40 (↑)	32 (N)
	BAP [µg/L]	27-83	31 (N)	63 (N)	63 (N)	49 (N)	52 (N)	63 (N)
	PINP [µg/L]	437-827	not done	338 (↓)	347 (↓)	237 (↓)	224 (↓)	223 (↓)
Serum	Ca [mmol/L]	2.17-2.49	2.32 (N)	2.36 (N)	2.41 (N)	2.28 (N)	2.13 (↓)	2.28 (N)
	PO_4 [mmol/L]	1.17-1.75	1.43 (N)	1.50 (N)	1.41 (N)	1.39 (N)	1.28 (N)	1.28 (N)
	25(OH)-Vit. D_3 [nmol/L]	50-92	58 (N)	102 (↑)	78 (N)	48 (↓)	65 (N)	95 (↑)
	1,25(OH)-Vit. D_3 [nmol/L]	91-234	231 (N)	216 (N)	224 (N)	200 (N)	185 (N)	200 (N)
2nd void urine	Ca/Crea [mmol/L / mmol/L]	<0.4	2.09 (↑)	2.75 (↑)	0.68 (↑)	2.32 (↑)	1.70 (↑)	0.92 (↑)
	PYR [µg/g creatinine]	370-510	783 (↑)	572 (↑)	706 (↑)	541 (↓)	603 (↑)	655 (↑)
	DPYR [µg/g creatinine]	62-83	180 (↑)	123 (↑)	149 (↑)	142 (↑)	139 (↑)	136 (↑)

Normal age-related (Tanner stage I) values for parathyroid hormone (PTH), osteocalcin, Ca, PO_4, 25-OH-Vitamin D_3 [25(OH)-Vit. D_3] and 1,25-(OH)-Vitamin D_3 [1,25 (OH) Vit. D_3] levels, bone-specific alkaline phosphatase (BAP), N-terminal propeptide of type I collagen (PINP), pyridinoline (PYR), and desoxypyridinoline (DPYR).[4,5]

has been achieved by imatinib.[6] However, in adults side-effects affecting bone metabolism were described in 2006 hypothesizing that unspecific inhibition of tyrosine kinases (c-KIT, PDGF-α, -β, c-FMS) which are either expressed by osteoblasts and osteoclasts may impair bone remodeling.[7] This mechanism was demonstrated to be active in adult mice.[8] Further reports providing evidence that imatinib treatment does affect bone metabolism followed rapidly.[9,10] Also in a model of juvenile mice, long-term imatinib treatment had an anti-resorptive effect on osteoclasts and impaired the length of tubular bone. These effects on the growing skeleton were more pronounced in prepubertal animals.[11]

Mariani *et al*. observed a 9-year old boy who developed impaired growth shortly after the start of imatinib treatment which resolved at the onset of puberty resulting in no deficiency of his prospective final height.[12] GH deficiency was excluded in this case but endocrinological abnormality in the form of a reduced inhibin B/FSH ratio was present. However, in contrast to other reports on findings in adults and animal data he exhibited reduced bone mineral density of his lumbar vertebrae as determined by DXA following six years of imatinib treatment.

Skeletal growth impairment is of major concern in pediatric patients. In the girl described here cumulative data of biomarkers of mineral and skeletal homeostasis showed a slight increase in bone turnover as the plasma osteocalcin level was elevated while bone formation was reduced as indicated by lowered plasma PINP. Urinary Ca excretion was increased as were the urinary concentrations of the collagen cross-links PYR and DPYR which are indicative of bone resorption. These alterations may not be attributed to the partial GH deficiency as in children with this disorder urinary concentration of PYR and DPYR is lower than in healthy controls.[13] Thus, these data suggest a prevalence of bone resorption over formation by which skeletal growth is affected resulting in the impressive cutting score of the length percentiles noticed. It is noteworthy that the growth of her two triplet siblings was unaffected. Whether catch-up growth at the onset of puberty as reported by Marani *et al*. will also occur in the girl reported here has to be studied in the future as she is still prepubertal.[9] The underlying partial GH-deficiency may represent a major obstacle to this hope. However, without standardized testing random GH measurements may be inconclusive.

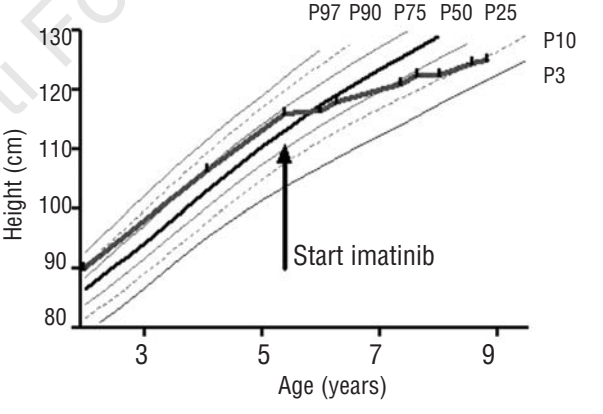

Figure 1. Decrease in body height under imatinib therapy (*percentiles according to Hesse, Jaeger, Vogel et al. 1997*).[3]

As the number of children with CML on long-term imatinib treatment is constantly increasing, so far unobserved and/or unreported side effects of this small molecule inhibitor may play a more important role in the future. As SCT may also result in growth impairment, the choice of the optimal treatment for pediatric CML remains an ongoing challenge.

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Risk of solid tumors and myeloid hematological malignancies among first-degree relatives of patients with monoclonal gammopathy of undetermined significance

Monoclonal gammopathy of undetermined significance (MGUS) is one of the most common pre-malignant disorders in western countries with a prevalence of 3.2% in the Caucasian general population 50 years of age or older.[1] It is characterized by the presence of a monoclonal immunoglobulin (M-protein) in individuals lacking evidence of multiple myeloma (MM) or other lymphoproliferative malignancies.[2] Long-term follow-up of MGUS patients reveals an average 1% annual risk of developing a lymphoproliferative malignancy.[3,4] Although the etiology of MM and MGUS is unknown, there is emerging evidence to support a role for genetic factors. For example, familial aggregation of both MM and MGUS has been observed.[5] Also racial disparities in incidence patterns for MGUS and MM support a role for germline genes in the etiology of MM.[6] Recently, we found first-degree relatives of MGUS patients to have an increased risk of MGUS, MM, lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia, and chronic lymphocytic leukemia, supporting a role for shared common germline susceptibility genes in these disorders.[5] Furthermore, in two recent studies an excess of certain solid tumors among blood relatives to MM patients was reported.[7,8]

To improve our understanding in this area, we have, to the best of our knowledge, conducted the first population-based study to evaluate familial aggregation patterns of 27 solid tumors and all myeloid hematologic malignancies among first-degree blood relatives of MGUS patients. Using high-quality population-based data from Sweden, we identified 4,458 MGUS patients and 17,505 controls, as well as all linkable first-degree

Table 1. Characteristics of MGUS patients and matched controls.

	MGUS patients	Controls
Total, n.	4,458	17,505
Gender male/female, %	49.9/50.1	50.0/50.0
Age at dx, median (range)	69 (22-97)	N.A.
Age group, n (%)		
Less than 40	118 (2.7)	471 (2.7)
40-49	328 (7.4)	1,321 (7.5)
50-59	749 (16.8)	3,008 (17.2)
60-69	1,091 (24.5)	4,236 (24.2)
70-79	1,389 (31.2)	5,389 (30.8)
80 and above	783 (17.6)	3,080 (17.6)
Calendar period, n (%)		
1966-1975	33 (0.7)	138 (0.8)
1976-1985	260 (5.8)	1,048 (6.0)
1986-1995	1,866 (41.9)	7,309 (41.7)
1996-2005	2,299 (51.6)	9,010 (51.5)
MGUS isotype, n (%)		
IgG	1,789 (40.1)	N.A.
IgA	482 (10.8)	N.A.
IgM	447 (10.0)	N.A.
IgD	1 (0.02)	N.A.
Unknown/missing	1,739 (39.0)	N.A.
First-degree relatives, n (%)		
Any relative	14,621 (100)	58,387 (100)
Parents	2,811 (19.2)	11,006 (18.9)
Siblings	2,290 (16.7)	8,962 (15.3)
Offspring	9,520 (65.1)	38,419 (65.8)