



A Third Case of Glycogen Storage Disease IB and Giant Cell Tumour of the Mandible: A Disease Association or Iatrogenic Complication of Therapy

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Abstract We report the third case of Glycogen Storage Disease type 1b (GSD 1b) with Giant Cell Tumour (GCT) of the mandible, associated with Granulocyte Colony Stimulating Factor (G-CSF) use. G-CSF in GSD 1b is indicated for persistent neutropaenia, sepsis, inflammatory bowel disease and severe diarrhoea. Our patient was 12 years old at GCT diagnosis and had been treated with

G-CSF from 5 years of age. He underwent therapy with interferon followed by local resection which was successful in initial control of the disease. Histology demonstrated spindle shaped stromal cells together with numerous interspersed multinuclear osteoclastic giant cells. G-CSF has been hypothesized to induce osteoclastic differentiation and thus may be involved in the pathogenesis of GCT formation. At age 19 years he required a repeat operation for local recurrence. He currently continues on G-CSF and was commenced on denosumab for control of the GCT with no recurrence to date. A cause and effect relationship between G-CSF therapy and the development of GCT in GSD type 1b remains to be established.

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Introduction

Glycogen storage disorder 1b (GSD 1b) is due to recessive mutations in the *SLC37A4* gene expressing glucose-6-phosphate translocase. In addition to hypoglycaemia, GSD 1b is complicated by hyperlipidaemia, hyperuricaemia, growth retardation, hepatosplenomegaly, renal dysfunction and neutropaenia with other hematologic abnormalities (Burda and Hochuli 2015; Chou et al. 2015). Here we report the third case associating GSD 1b and Giant Cell Tumour (GCT) of the mandible while the patient was on Granulocyte Colony Stimulating Factor (G-CSF).

Case Report

Our patient was born following a normal pregnancy at term weighing 3.3 kg. He had transient hypoglycaemia in the

newborn period and was discharged home on day 14 of life. He represented at age 5 months with a diarrhoeal illness and hypoglycaemia. Hepatomegaly was noted at that time. Following a number of further admissions with hypoglycaemia during intercurrent illness, a liver biopsy was performed which reportedly demonstrated glycogen storage disease (although the details of this result are not available to us). Persistent neutropenia was apparent in the first year of life. Genetic sequencing demonstrated an apparently homozygous variant reported as pathogenic in the *SLC37A4* gene (c.1179G>A; p.Trp393*). Metabolic control was not optimal during the first years of life, with multiple hospital admissions and documented hypoglycaemia. Disease complications have included episodes of hypoglycaemia leading to intellectual disability, multiple episodes of sepsis, neutropenia, haemolytic anaemia, splenectomy and multiple hepatic adenomas. G-CSF was commenced at 5 years of age. His current dose of G-CSF is 300 mcg (5 mcg/kg) four times weekly, with Australian guidelines (Australian Medicines Handbook) suggesting 5 mcg/kg daily in cases of idiopathic or cyclic neutropenia.

He was diagnosed with GCT of the mandible at age 12 years. Interferon therapy for post excision management of his tumour was continued for 3 years post resection. He re-presented with increased gum bleeding 7 years later. A CT and biopsy of the site confirmed recurrence and tumour excision surgery was performed. Histology of the lesion revealed large giant cells consistent with giant cell tumour (Figs. 1 and 2). He has been placed on denosumab therapy for postoperative control of the giant cell tumour.

Discussion

GSD 1b and GCT of the mandible have previously been described in two other patients (Mortellaro et al. 2005; Amaral et al. 2009). Both were receiving G-CSF at the time of tumour occurrence. To our knowledge, this is the third case of a patient with GSD 1b and a giant cell tumour on G-CSF, suggesting a causative association.

Giant cell granulomas of the jaw are benign, locally aggressive tumours of the jaw of unknown aetiology but their occurrence has been observed in Neurofibromatosis type 1, Noonan syndrome and cherubism (O'Connell et al. 2015). These lesions arise from the supporting connective tissue of the marrow and are characterised histologically by ovoid stromal or spindle shaped cells interspersed with multinuclear cells and tend to recur locally despite surgery (Amanatullah et al. 2014; O'Connell et al. 2015).

Although the origins of giant cell tumours are unclear, it has been suggested that they may be derived from osteoclast progenitors (Liu et al. 2003). It has been hypothesized that long term use of G-CSF promotes osteoclastogenesis resulting in giant cell tumours (Amaral et al. 2009). G-CSF activates extracellular membrane receptors such as *c-fms*. These receptors then activate a signalling pathway that differentiates progenitor myeloid cells into osteoclasts (Kitaura et al. 2005).

It is interesting to note that the other two cases of GSD 1b who developed giant cell tumours were also on G-CSF (Mortellaro et al. 2005; Amaral et al. 2009). While generally accepted to be safe, a potential for carcinogenicity

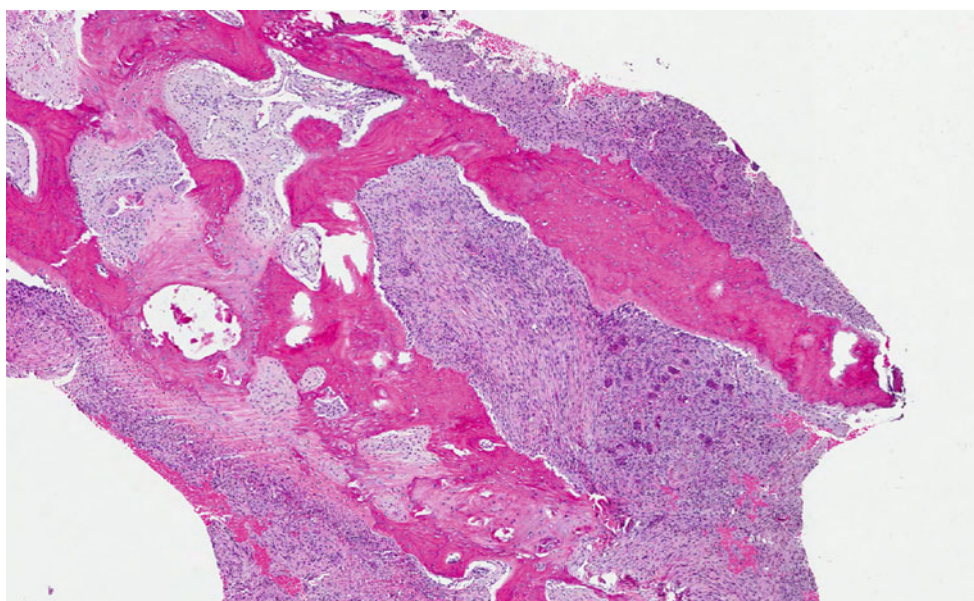


Fig. 1 Low power magnification (4× objective) of giant cell tumour of the mandible showing a giant cell lesion

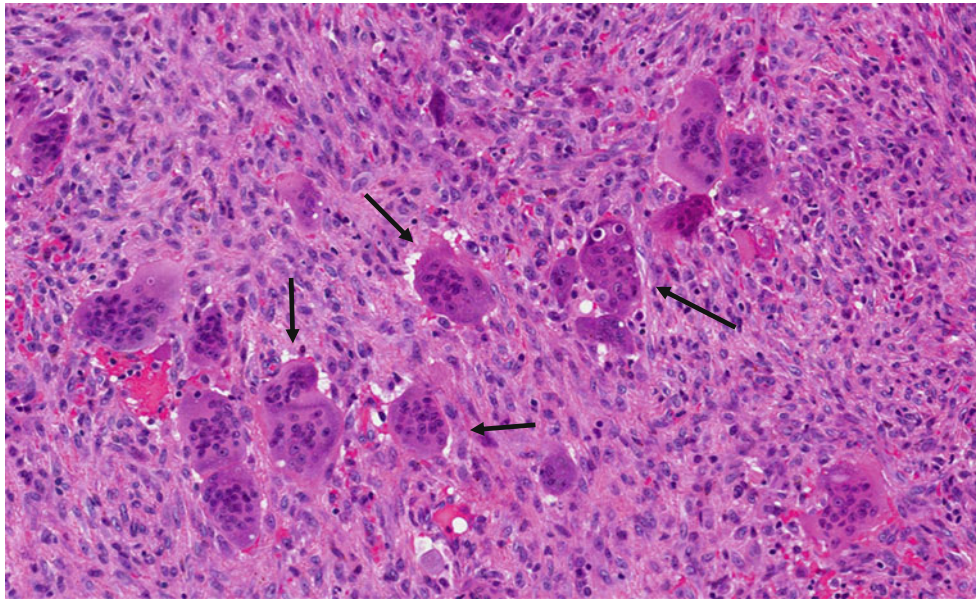


Fig. 2 Histological features of the giant cell tumour of the mandible at high power magnification (40× objective) showing large multinuclear cells in the stroma of the mandible with prominent inclusions (arrows)

due to the presence of G-CSF receptors in tumour cell lines exists (Schipperus et al. 1990). There have been reports of three patients with GSD 1b developing acute myelogenous leukaemia, two on G-CSF and one not on G-CSF (Simmons et al. 1984; Pinski et al. 2002; Schroeder et al. 2008). In fact, previous consensus guidelines for GSD 1 management included annual bone marrow examination with cytologic studies in patients on G-CSF, although this is no longer included in the current consensus guidelines (Visser et al. 2002; Kishnani et al. 2014). The role of GSD1b and resultant aberrant glycogen in GCT tumorigenesis remains to be defined.

We also consider the possibility that the periodontitis and resulting chronic inflammation, as well as the aberrant glycogen seen in GSD1b may represent an additive effect together with G-CSF that results in abnormal cellular differentiation and growth. Oral manifestations of GSD 1b (periodontitis, recurrent oral ulceration, bleeding diatheses and dental caries) are thought to be related to neutropaenia and/or neutrophil dysfunction; similar oral manifestations are seen in other neutropaenic states (Barrett et al. 1990). This case of GCT in a patient with GSD1b on G-CSF highlights a possible association, and indicates that vigilance for this disease complication is warranted.

Conclusion

We describe the third reported case of GCT of the mandible recurring in a patient with GSD1b whilst the patient was on

G-CSF therapy. Histology and imaging supported the diagnosis of GCT of the mandible. It remains to be established whether there is a cause and effect relationship between G-CSF therapy and the development of GCT in GSD type 1b.

Conflict of Interest

Raajiv Prasad, Jane Estrella, John Christodoulou, Geoffrey McKellar and Michel C. Tchan have no disclosures related to this manuscript.

Informed Consent

Informed consent was obtained from the patient and his parents for being included in this study.

Contributions of the Individual Authors

Raajiv Prasad and Jane Estrella have contributed equally to the writing of this manuscript. All authors have contributed to the planning, conduct and reporting of the work described in this chapter and all authors have approved the manuscript.

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