been substantially curtailed this millennium following the introduction of recombinant G-CSF.⁷ Although no randomised study has successfully demonstrated a survival advantage for patients receiving GT, clinical outcomes have been reported in retrospective and prospective case series, suggesting that clinical improvement for bacterial infections can be achieved when sufficient GT neutrophil doses are delivered. However, outcomes for GT in IFD are heterogeneous at best, and have been reported as showing minimal clinical benefit and occasional potential detriment.⁸ There remains no consensus about the overall clinical efficacy of GT in the treatment of infection, perhaps representing a lack of evidence rather than lack of benefit.

While GT is occasionally used in crisis situations such as our patient's case, its clinical utility has often been limited by transfusion-related factors. Firstly, GT carries risks of immune-mediated transfusion reactions such as TRALI and transfusion-associated graft versus host disease (TA-GVHD). Secondly, the short lifespan of the transfused granulocytes, exacerbated by the irradiation performed to prevent TA-GVHD, results in a need for repeated infusions to achieve clinical impact. Thirdly, GT source also impacts upon deliverability: although granulocyte yield is significantly higher from a directed-donation leukapheresis than from a single whole blood derived BC collection, extended GT treatment such as that required by our patient is rarely sustainable or feasible from directed donation, and is extremely labour-intensive for apheresis and transfusion services.

Reports of GT for IFD in CGD typically are sporadic doses given over a 1–4 week period, ceased either due to neutrophil recovery from prior chemotherapy, severe transfusion reaction, or patient death from IFD. The largest series in the literature reported a median 2–6 GT in 28 patients, resulting in an overall response rate of 82% with 1% incidence of transfusion reactions;⁹ the previously maximum reported dose and duration by any patient in the literature is three times a week for 2 months.¹⁰ Adoptive cell therapy (ACT), which involves the infusion of donor-derived pathogen-specific T cells, has been explored as a potential treatment option in patients with severe infections who are profoundly immunocompromised.¹¹ This may be a future treatment modality for CGD patients with life-threatening IFD. Our case, which clearly exceeds the previous maximum reported treatment of GT for any infection, highlights the potential benefit for extended GT treatment in IFD, and the potential benefits in terms of utility and feasibility of using BC as GT source, without apparent compromise in terms of transfusion safety or alloimmunisation. However, this should only be limited to last resort therapy.

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Systemic mastocytosis associated with two clonal haematological neoplasms

Sir,

Systemic mastocytosis with an associated haematological neoplasm (SM-AHN) is recognised by the 2017 World Health Organization (WHO) classification as a subtype of SM and requires both criteria for SM and AHN to be met as distinct entities.¹ The second non-mast cell malignancy is generally of myeloid origin with chronic myelomonocytic leukaemia (CMML) being the most common.^{1,2} Other studies have also described the second myeloid neoplasm harbouring the malignant mast cells. There are a few reports of lymphoid neoplasms such as multiple myeloma or lymphoma being associated with SM.^{1,2} In our correspondence, we describe a case of SM associated with two clonal haematological neoplasms, one myeloid and the other a primary plasma cell neoplasm.

A 72-year-old male with severe osteoporosis was found to have an IgM lambda paraprotein of 9 g/L on screening tests. A bone marrow biopsy performed showed less than 10% lambda light chain restricted plasma cells, consistent with a diagnosis of IgM monoclonal gammopathy of undetermined

significance (MGUS). Concurrently, multifocal aggregates of abnormal and spindle-shaped mast cells were present and the *KIT* D816V mutation was detected. The mast cell tryptase level was raised at 45.6 µg/L (<11.4 µg/L). A diagnosis of SM-AHN was made. In particular, the patient did not have any mediator release symptoms, cutaneous manifestations or end organ damage and his management was observation only.

Over the following 3 years the patient remained well, the IgM paraprotein stable at 9 g/L but his platelet count increased from $398 \times 10^9/L$ to $764 \times 10^9/L$; the *MPL* W515K mutation was detected. A repeat bone marrow biopsy showed persistence of the mast cell aggregates (Fig. 1A and 2A) and the low level plasmacytosis (Fig. 2B). In addition, there were new findings of megakaryocytic hyperplasia and interstitial clusters. There were large megakaryocytes with hyperlobated nuclei and emperipolesis was present, in keeping with a diagnosis of essential thrombocythaemia (ET) (Fig. 1B). Reticulin was normal (WHO grade MF-0). He was commenced on aspirin and hydroxyurea for his ET. He continued to be observed from the IgM MGUS point of view and received regular bisphosphonate therapy for his osteoporosis.

There are two novel findings in this case. Firstly, there are two separate clonal haematological neoplasms associated with SM, i.e., IgM MGUS and ET; secondly, to our knowledge, the occurrence of SM with *MPL* mutated ET has not been previously reported. In a review by Cancian *et al.*, only

15 other cases of SM with ET were described in the literature, and in those who were tested, they generally harboured the *JAK2* V617F mutation.³ These cases had skin or bony lesions at the time of diagnosis and cytoreductive therapy such as hydroxyurea or interferon were commonly utilised for the management of ET.³ A case report of coexistent systemic mastocytosis and *JAK2* negative ET and MGUS was previously published in 2012, however other molecular markers for MPN were not tested.⁵ SM associated with a plasma cell dyscrasia is also very rare, and only isolated reports of up to 9 cases have been described.⁴

At the molecular level, SM is linked to the somatic gain-of-function point mutation within *KIT*, a type III receptor tyrosine kinase that binds to stem cell factor (SCF), which plays a key role in regulating mast cell proliferation, maturation, adhesion, chemotaxis and survival.² The *KIT* D816V mutation is implicated in over 95% of adult SM.² On the other hand, the *MPL* gene encodes the thrombopoietin receptor and influences key growth and survival factor for megakaryocytes and mutated *MPL* results in an acquired gain of function resulting in the constitutive, cytokine independent activation of the JAK-STAT pathway.⁶ The *MPL* mutation is present in 3–4% of patients with ET.^{1,6}

The pathophysiological relationship between mast cell proliferation and associated myeloid haematological malignancies is not well defined, although studies have indicated it is likely both arise from a common pluripotent haematopoietic stem cell origin.² Sotlar *et al.* have demonstrated

Fig. 1 Bone marrow trephine (H&E stain). (A) Mast cell aggregate of SM with admixed eosinophils. (B) Megakaryocytic hyperplasia with clustering and large abnormal forms, features of the ET.

Fig. 2 Bone marrow trephine biopsy immuno-peroxidase stain. (A) Mast cell tryptase positivity of the mast cell aggregates. (B) Plasma cells of the MGUS positive for CD138.

that in SM and myelofibrosis, microdissected mast cells harboured both the *KIT* and *JAK2* V617F mutations in four of five patients, and microdissected CD15+ myeloid cells had both the *KIT* and *JAK2* V617F mutations in one of five patients. This implies that both molecular defects can be expressed in both components of the disease.⁷ Recent data have also identified additional molecular abnormalities, including *SRSF2*, *ASXL1*, *RUNX1* and *TET2* mutations, which are often acquired by neoplastic stem cells prior to *KIT* mutation, suggesting a multi-mutated stem cell disease and step-wise process of oncogenesis.⁸ In 45% of core binding factor AML the *KIT* D816V mutation is also present⁸ and reports of the pathogenic leukaemic translocation t(8;21) being detected in the neoplastic mast cells also hint that the mast cells may have developed from the leukaemic clone.⁹

In contrast, SM with coexisting lymphoid or plasma cell malignancies are thought to be clonally separate as the *KIT* D816V mutation present in the neoplastic mast cells has not been detected in malignant lymphocytes.¹⁰ Neoplastic mast cells are known to be a source of multiple cytokine production and *in vitro* studies have demonstrated that the cells are able to support the growth of malignant lymphoid cells through CD154-CD40 signalling and plasma cells via the production of cytokines such as IL-1, IL3, IL-6 and SCF.¹¹ Identification of oligoclonal immunoglobulin bands in the sera of some patients with SM also indirectly supports the notion that there is increased proliferation of plasma cells through neoplastic mast cells.¹¹ It is also possible that there is no pathophysiological link between the SM and IgM MGUS. As the prevalence of MGUS increases with age, with up to 4.5% of patients aged 70–79 having a diagnosis of MGUS, the association with SM in this patient may be an incidental finding.¹² Further, the ET evolved over time as it was not evident at the time of the IgM MGUS or SM diagnosis given the initial normal platelet counts.

Lastly, this case also highlights the importance of careful inspection of other cell lineages not affected by SM and the need for ongoing monitoring for the development of other haematological malignancies.

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Thinking fast not slow: a fast-acting, high-titre acquired factor VIII inhibitor

Sir,

A 45-year-old male was brought to the emergency department in February 2020 following a long lie with a reduced level of consciousness. The patient had a past medical history of relapsing remitting multiple sclerosis (MS), diagnosed in August 2016 following a step-wise deterioration in gait and mobility over 16 months. His MS was initially managed with fingolimod. In August 2017, radiological disease progression on magnetic resonance imaging mandated escalation of disease modifying therapy and a first cycle of alemtuzumab was administered without complication. A second cycle of alemtuzumab followed in August 2018.

On examination, he had bruising and swelling of both the right knee and ankle. Ultrasound imaging was consistent with a right suprapatellar bursa haematoma and haemarthroses of the right knee and ankle joints. A computed tomography scan of the brain did not reveal evidence of an acute intracranial haemorrhage.

Investigations noted a normal full blood count (Table 1). His prothrombin time was 14.9 s, international normalised ratio 1.0 and activated partial thrombin time (APTT) prolonged at 98 s. The patient had no history of heparin or direct oral anticoagulant use. Immediate and extended mixing studies were performed. The immediate 1:1 APTT mix was 91 s with minimal change after extended incubation, indicating the presence of a fast-acting inhibitor. A lupus anticoagulant (LA) screen was negative by dilute Russell's viper venom time. The LA screen by high and low phospholipid APTT reagents showed a clear positive ratio. However, the incomplete correction of the clotting time to normal by the high phospholipid reagent was a clue that an inhibitor other than a LA may be present.