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Successful use of allogeneic bone marrow transplantation in a patient with myelodysplastic syndrome presenting with autoimmune manifestations

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MDS is a clonal haematopoietic disorder, characterised by ineffective haematopoiesis and peripheral blood cytopenias [(1)]. There is a widely recognised association of MDS with autoimmune symptoms, with an incidence reported between 10-20% [(3)]. Here, we discuss a patient presenting with multiple treatment-refractory autoimmune manifestations (AIMs), which preceded the diagnosis of MDS and culminated in the patient requiring an allogeneic bone marrow transplant (allo-BMT).

A 56-year-old Caucasian male with no preceding history of autoimmune disease presented in April 2018, complaining of a widespread relapsing-remitting maculopapular rash, joint pain and proximal muscle weakness, associated with systemic symptoms (fever and lethargy). The rash appeared symmetrical and involved the face, torso, neck and proximal limbs (Figure 1A, B). Blood tests revealed a macrocytic anaemia (Hb 110 g/L, MCV 100 fL), which had been present since May 2011.

Initially diagnosed with erythema multiforme, he was commenced on oral prednisolone 40 mg daily. Despite initial improvement, over the next 12 months, he continued to experience intermittent rashes, low-grade pyrexia, lethargy, joint pain and progressive weight loss. By June 2018, he had developed worsening anaemia (Hb 80 g/L, MCV 106 fL), leukopenia of 2.8 $x10^9$/L (neutrophils 1.68 $x10^9$/L) and raised inflammatory markers. An autoimmune screen showed mildly reduced complement levels, C3 0.10 g/L (NR 0.16-0.48 g/L) and C4 0.63 g/L (NR 0.8-1.6g/L), weak positive p-ANCA, mildly positive rheumatoid factor of 16 IU/ml (NR 0–12 IU/ml) and anti-cardiolipin IgM antibody of 17 mplu/ml (NR 0-12mplu/ml). A CT chest-abdomen-pelvis was unremarkable. During this time, he was frequently requiring prednisolone (0.5mg/kg) to control his symptoms.

A bone marrow aspirate undertaken in July 2018 was hypercellular with features of erythroid and megakaryocytic dysplasia but no increase in blasts. A trephine biopsy was also hypercellular (80%) with architectural disarray, increased reticulin staining (grade 1-2) without significant para-trabecular fibrosis. Next generation myeloid sequencing (Illumina Myeloid Panel, NGS) highlighted 2 pathogenic mutations: ASXL1 (NP_056153.2:p.Asp1032ValfsTer15) and SRSF2 (NP_003007.2:p.Pro95His), with variant allele frequencies of 49% and 37%, respectively. Based on these results, a diagnosis of primary MDS was established [(1)]. IPSS-R score [(2)] was 3, with an age-adjusted score of 2.

He subsequently progressed to develop profound bilateral leg weakness and hip pain. An MRI showed foci of oedema-like signal within the thigh muscles, in keeping with myositis (Figure 1C). A Rheumatology review concluded his symptoms were suggestive of atypical dermatomyositis, possibly attributable to the MDS. A skin biopsy was performed, which proved inconclusive. He remained anaemic and now occasionally required red cell transfusion support despite erythropoietin treatment (Figure 1D). Given his now chronic steroid-dependence, he was treated with immunosuppression using anti-thymocyte globulin (ATG) and cyclosporine. However, there was again relapse of his constitutional, muscle and skin symptoms on reduction of prednisolone and persistence of his anaemia.

In view of the severity and chronicity of his symptoms and the concurrent diagnosis of MDS requiring intermittent transfusion support, in a young fit patient, we elected to perform an allo-BMT. Tissue typing identified a 10/10 HLA male sibling donor and he underwent a reduced intensity conditioned stem cell transplant (HSCT) with fludarabine (30 mg/m^2/day on days -7 to -3), melphalan (140 mg/m^2 on day -2) and alemtuzumab (20 mg/day on days -8 to -4 for in vivo T-cell depletion) in April 2019.
His post-transplant course was complicated by persistent stage 2 chronic skin graft-versus-host-disease (GvHD), requiring extra-corporeal phototherapy. At 3 months post-transplant, peripheral blood showed 91% T-cell donor chimerism. Post-transplant NGS showed no evidence of the prior pathogenic ASXL1 and SRSF2 mutations. He is currently transfusion-independent, has been weaned off steroid completely, does not require any analgesia and has no further systemic symptoms. He remains on mycophenolate mofetil and cyclosporine as treatment for chronic GvHD.

Our case highlights several interesting points. Firstly, the true chronology of the autoimmune symptoms and the MDS diagnosis is difficult to establish. Our patient had a long history of AIMs prior to presentation, but he also had a 'smouldering' borderline MCV for at least 6 years. This is particularly significant as several observational studies suggest that chronic immune stimulation can promote the development of myeloid malignancies [4-6]. AIMs can occur before, during, or after the diagnosis of MDS, as reported in a recent retrospective cohort study from Mekinian et al.[7].

Secondly, this patient had a plethora of symptoms, including myositis, which is a rarely described manifestation, accounting for only 4% of patients in one series [8].

Thirdly, a proportion of MDS patients have severe, recalcitrant and progressive autoimmune features. It is in this group of patients that HSCT represents an alternative therapeutic strategy, which may offer sustained remission by more potent eradication of auto-reactive T-cells and development of self-tolerance [9]. Overall, only 0.1% of allo-BMTs are performed for primarily autoimmune disease [10]. There is limited data on the incidence of allogeneic transplantation performed for autoimmune disease associated with MDS, but case reports are described [11-12].

Finally, our case raises the important question of whether the presence of autoimmune symptoms has prognostic significance and whether MDS-associated cytogenetic or molecular aberrations may have increased the chance of developing AIMs.

Overall, it appears that AIMs tend to cluster more often in patients with higher-risk MDS. A statistically significant association between trisomy 8 and a Behçet-like syndrome has been described [8]. A systematic review of the genetic mutations associated with autoimmune disease identified the association of TET-2 mutations in patients with MDS [13]. TET-2 has been shown to play an important role in Th1 and Th17 differentiation of naïve CD4 T-cells, [14] which demonstrates that canonical myeloid mutations may also have effects on T-cell immunity. A case series of 3 patients with MDS and an SRSF2 mutation presenting with erythematous rash and systemic symptoms is noteworthy, suggesting this molecular subtype may cluster in patients with AIMs [15].

In conclusion, the combination of unexplained autoimmune symptoms with concurrent anaemia, particularly if macrocytic, should raise suspicion regarding a possible diagnosis of MDS with AIMs. Allo-BMT may be an effective treatment strategy in severe, treatment-refractory, recalcitrant autoimmune symptoms associated with MDS in young, fit patients with suitable donor options.

Authors contributions

GS (written, literature review, editing), SM (editing, literature review), SG (data collection), XP (editing), JM (editing), EP (editing, literature review).

Declarations

GS, SM, XP, SG, JM and EP - none.

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Figures

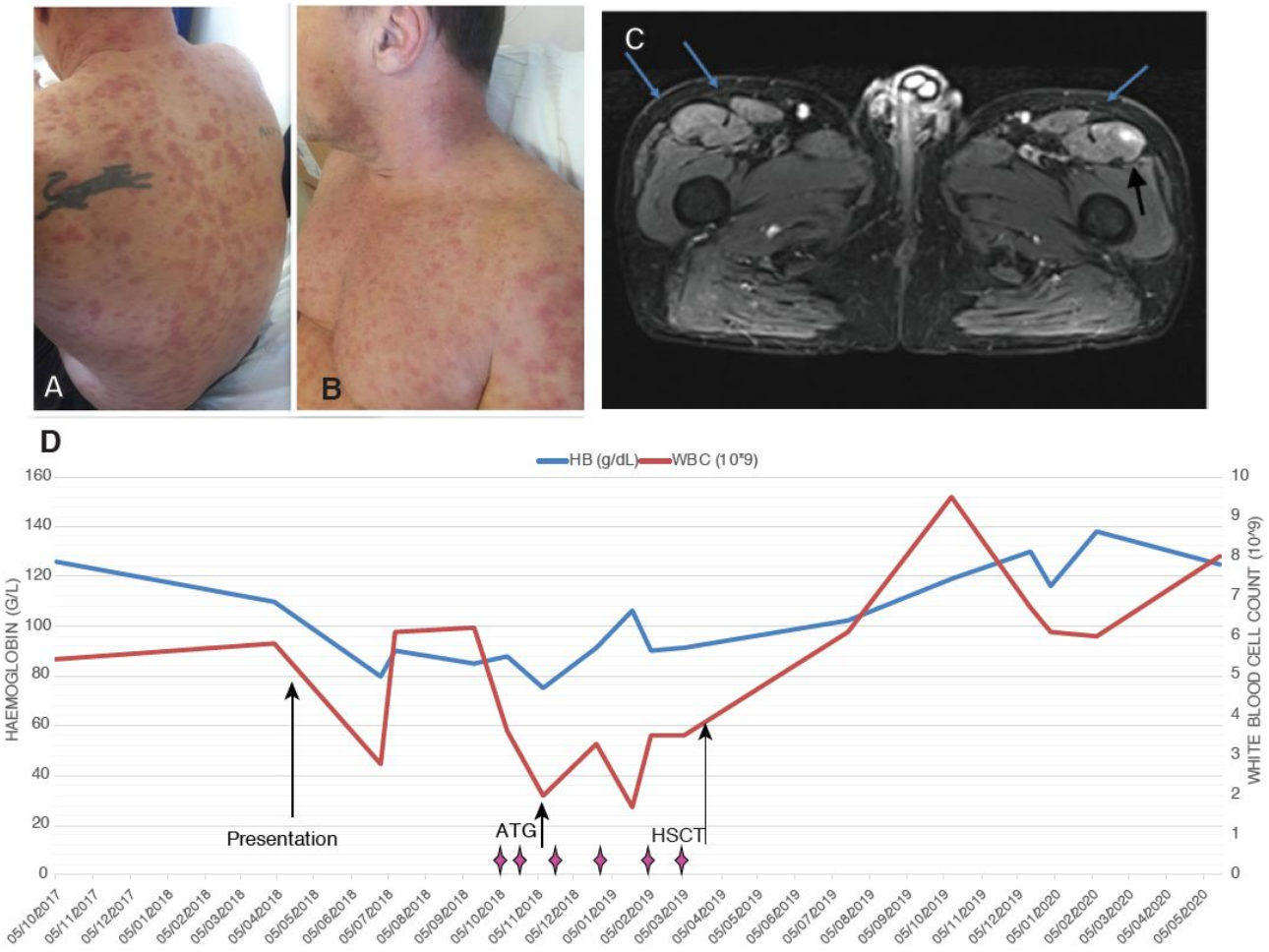

Figure 1. A & B *Maculopapular rash on presentation involving the neck, torso, arms and legs (proximally).* ***C****. Axial STIR MRI images of proximal hips. Blue arrows: foci of oedema-like signal within the thigh muscles, most prominent in the rectus femoris, semimembranous and semitendinous muscles bilaterally, in keeping with myositis. Black arrow: 10x8 mm fluid signal focus within the proximal left rectus femoris muscle, representing a small intra-muscular collection.* ***D****. Trend of Hb and WBC from May 2017 to April 2020. Pink diamonds show transfusion episodes.*

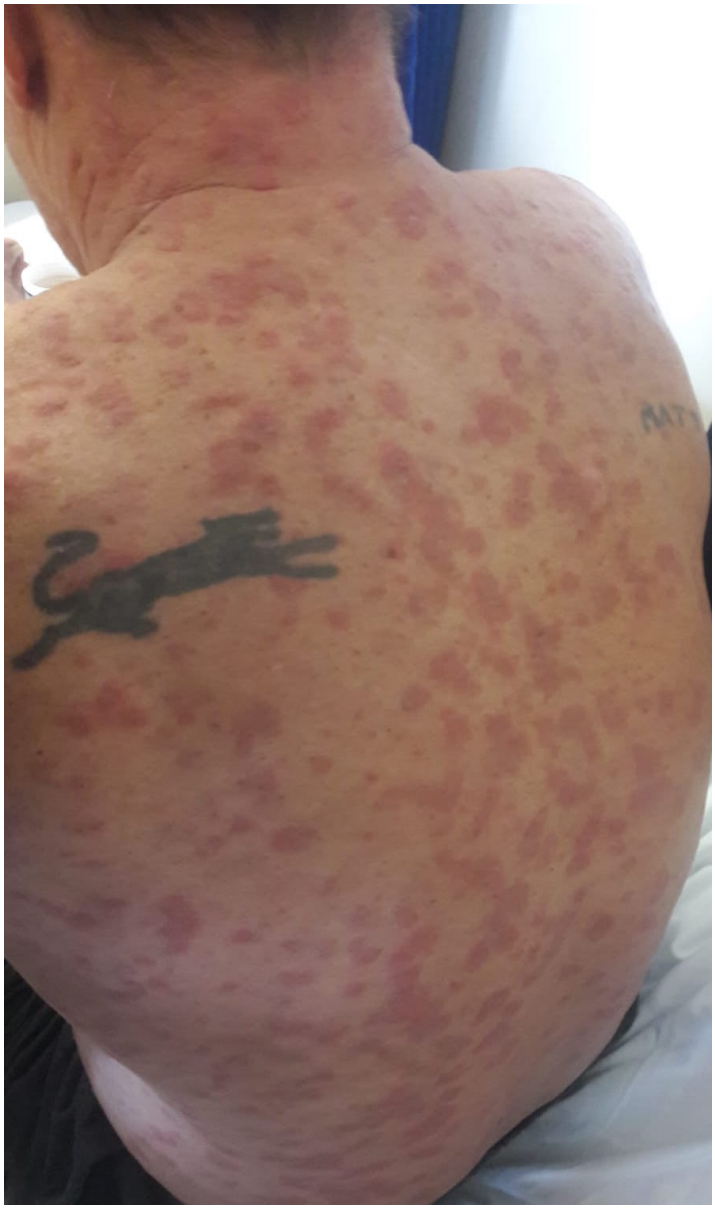

Figure 1A: maculo-papular rash on presentation involving neck, torso, arms and legs (proximally).

315x533mm (72 x 72 DPI)

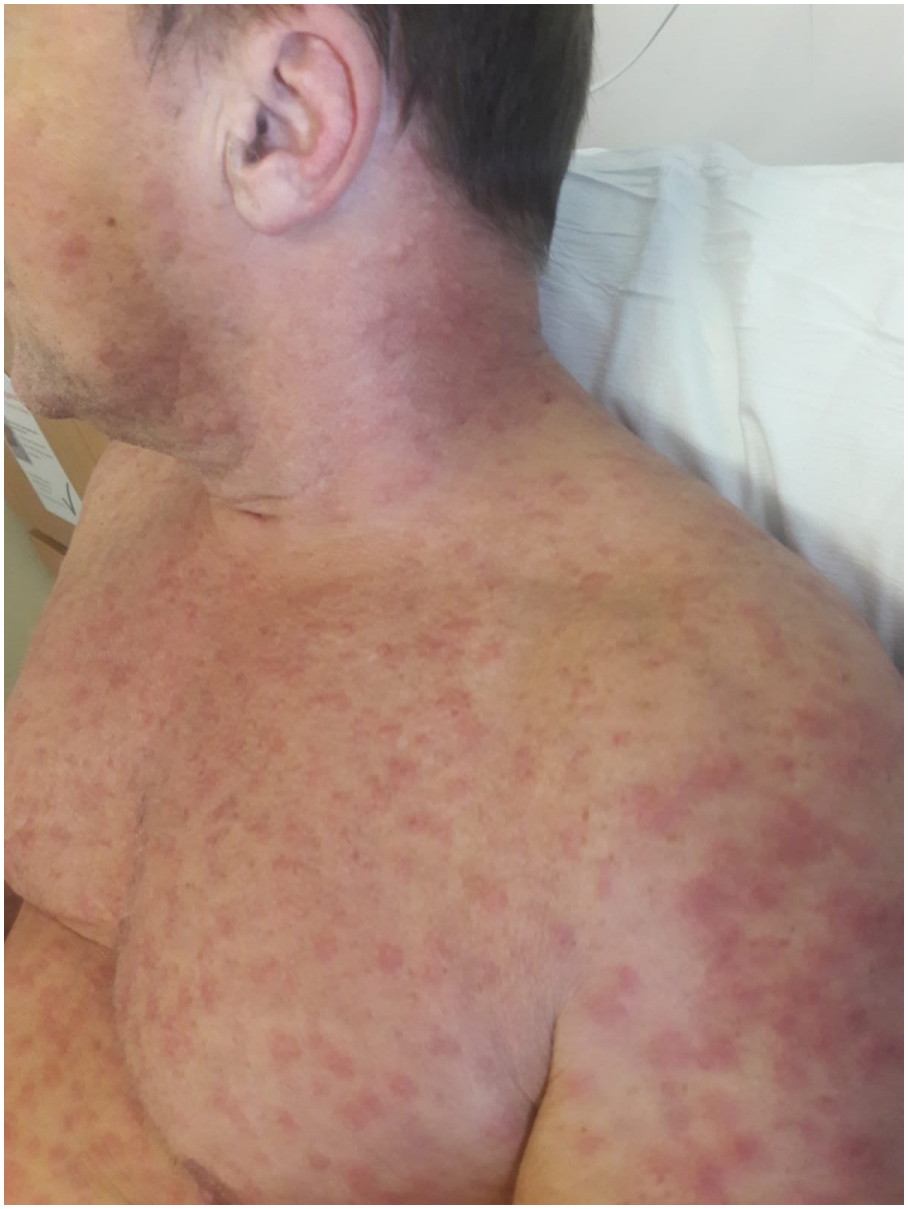

Figure 1B: maculo-papular rash on presentation involving neck, torso, arms and legs (proximally).

423x564mm (72 x 72 DPI)

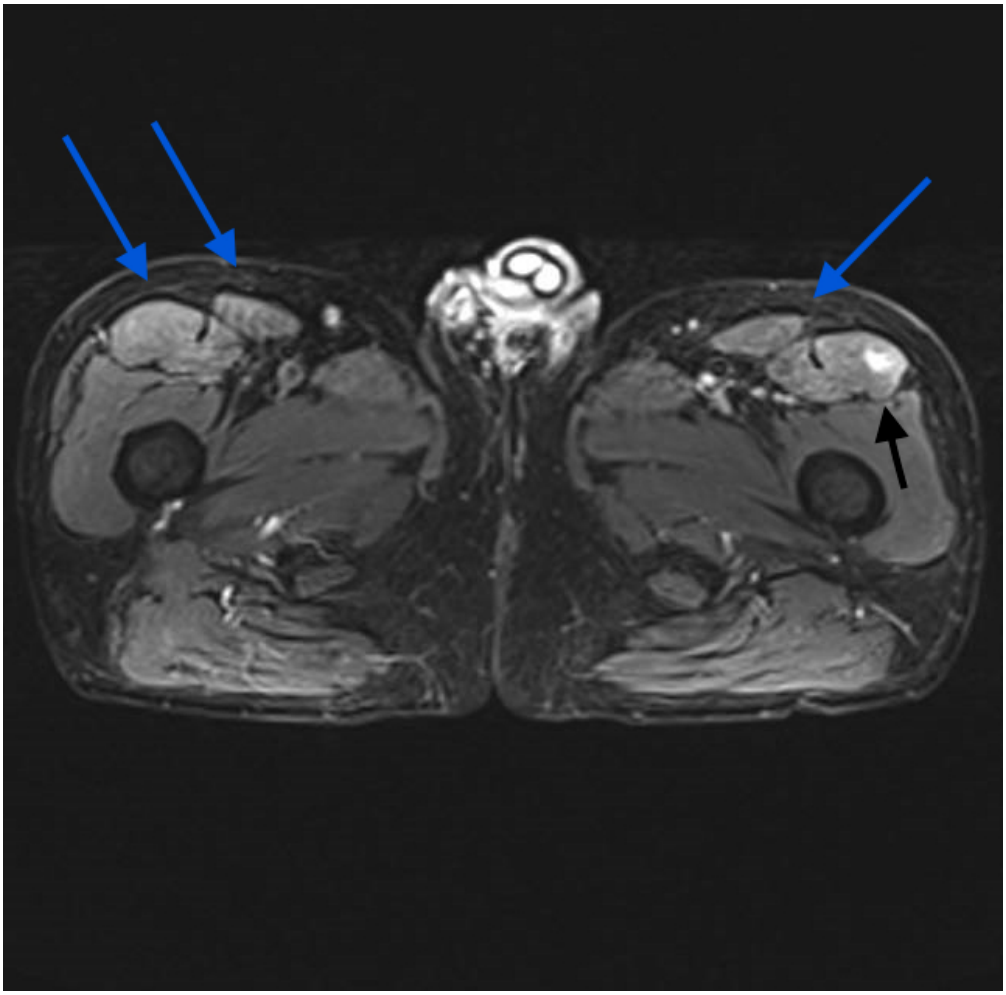

Figure 1C: MRI scan. Blue arrows: foci of oedema-like signal within the thigh muscles, most prominent in the rectus femoris, semi membranous and semi tendinous muscles bilaterally, in keeping with myositis. Black arrow: 10x8 mm fluid signal focus within the proximal left rectus femoris, representing a small intra-muscular collection.

226x223mm (72 x 72 DPI)

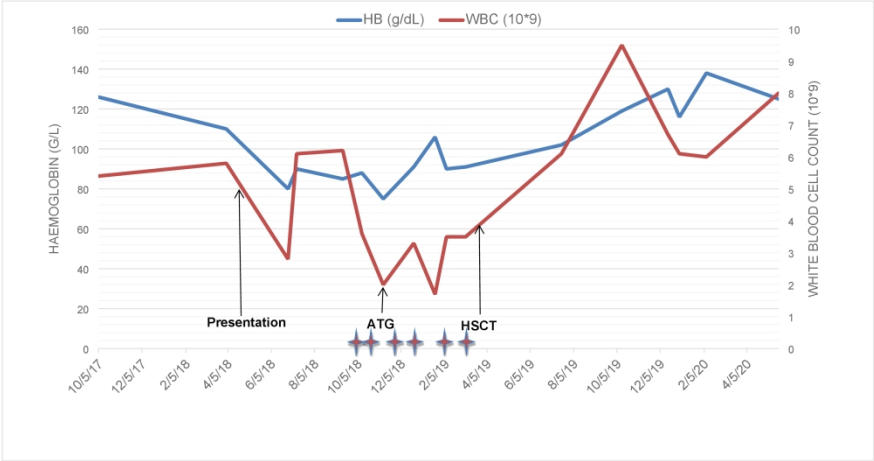

Figure 1D: trend of HB and WBC from May 2017 to April 2020. Pink diamonds show transfusion episodes.