



Figure 1. A) In this patient with alopecia areata, hair growth is exclusively noted within psoriatic plaques involving the scalp. B) Similar plaques of rupioid psoriasis on the legs.

play a key role in the competition between the two concomitant immune responses [1]. Thus, we postulate that in our patient, the psoriatic inflammation antagonized the inflammatory mechanism operating in AA [5]. The term “duelling cytokines” has been proposed to describe these complex interactions [6]. In our experience and that of others, psoriasis is less common among DS individuals [1-3], whereas AA is rather frequently noted and is often severe [1, 2].

Prior to our observation, only one case of a 20-year-old man with DS, presenting the Renbök phenomenon, has been described. AA occurred first and was then followed by psoriasis [6]. Conversely, in a young woman, remission of psoriasis and induction of AA was observed; the reappearance of psoriasis was then accompanied by hair growth [5].

In conclusion, individuals with DS may suffer from several dermatoses. The Renbök phenomenon, however, is a rarely observed and intriguing event. ■

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1. Schepis C, Barone C, Siragusa M, Pettinato R, Romano C. An updated survey on skin condition in Down syndrome. *Dermatology* 2002; 205: 234-8.
2. Madan V, Williams J, Lear JT. Dermatological manifestations of Down's syndrome. *Clin Exp Dermatol* 2006; 31: 623-9.
3. Schepis C, Barone C, Lazzaro Danzuso GC, Romano C. Alopecia areata in Down syndrome: a clinical evaluation. *J Eur Acad Dermatol Venereol* 2005; 19: 769-70.
4. Garnacho-Saucedo GM, Salido-Vallejo R, Alvarez-López MÁ R, et al. Renbök phenomenon in a patient with alopecia areata universalis. *Arch Dermatol* 2012; 148: 964-5.
5. Ovcharenko Y, Serbina I, Zlotogorski A, Ramot Y. Renbök phenomenon in an alopecia areata patient with psoriasis. *Int J Trichology* 2013; 5: 194-5.
6. Wylie GR, Burden D. Renbök phenomenon between psoriasis and alopecia areata. *Clin Exp Dermatol* 2011; 36: 816-7.
7. Happle R, van der Steen P, Perret C. The Renbök phenomenon: an inverse Köbner reaction observed in alopecia areata. *Eur J Dermatol* 1991; 1: 228-30.

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Azathioprine combination therapy for steroid-refractory hepatic immune system-related adverse events

Enhancement of anti-tumour immunity has led to substantial progress in the treatment of melanoma. Two types of immune checkpoint inhibitors, ipilimumab, targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and pembrolizumab and nivolumab, targeting programmed cell death-1 (PD-1), are now available.

Treatment with these agents can cause immune system-related adverse events (IRAEs) that manifest as pneumonitis, colitis, pancreatitis, hypothyroidism or hepatitis (*i.e.* hepatic IRAE) [1-3]. Nivolumab indications for advanced malignancies, in addition to unresectable or metastatic melanoma, including non-small cell lung cancer, renal cell carcinoma and Hodgkin lymphoma, reveal a potential increase in IRAEs. The majority of IRAEs can be managed with steroids; those refractory to steroid treatment can become life-threatening [4-6]. Although the purine antagonist mycophenolate mofetil (MMF) is recommended by its manufacturer for steroid-refractory hepatic IRAE [4], the supporting evidence is limited [5]. The American Association for the Study of Liver Diseases (AASLD) guidelines recommend the purine antagonist azathioprine (AZA) for treatment of steroid-refractory autoimmune hepatitis (AIH) cases, as an evidence-based regimen [7]. Herein, we present

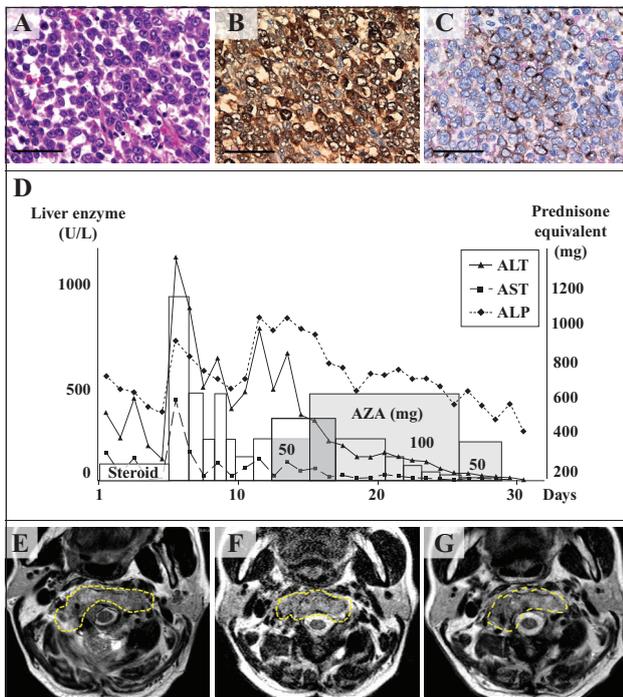


Figure 1. Histological findings of the vertebral tumour. **A)** Hematoxylin and eosin staining shows tumour cells with pale to clear cytoplasm and large atypical nuclei with conspicuous nucleoli. Immunohistochemical staining revealed positivity for S100 protein (**B**) and Melan-A (**C**). The graphical representation of the patient's clinical course (**D**) shows serum alanine amino transferase (ALT: solid line with triangles), aspartate transaminase (AST: dashed line with squares), and alkaline phosphatase (ALP: dotted line with diamonds). Prednisone-equivalent doses of steroid are shown as white columns, and the doses of oral azathioprine (AZA) are shown as grey bars. Magnetic resonance images (T2W1) of the vertebral tumour (**E-G**) are encircled by dashed lines; (**E**) before nivolumab administration; (**F**) after 10 cycles (2 mg/kg/3 weeks) of nivolumab treatment; (**G**) two months after the cessation of nivolumab and immunosuppressive regimens. The area of the tumour was quantified using ImageJ software, and is 0.56 in (**F**) and 0.84 in (**G**), relative to (**E**).

a case of nivolumab-induced hepatic IRAE, successfully treated with AZA.

A 75-year-old Japanese man with posterior cervical pain visited an orthopaedic hospital. Magnetic resonance imaging (MRI) revealed multiple tumours of the cervical and thoracic vertebrae suggesting injury to the cervical spinal cord (figure 1E). Posterior decompression surgery and a biopsy performed two months later yielded a diagnosis of metastatic melanoma (figures 1A-C). No primary site was found on positron emission tomography/computed tomography (PET-CT).

After referral to our clinic, 2 mg/kg of nivolumab at three-week intervals was started. After 10 cycles, the patient developed general fatigue and elevated serum alanine amino transferase (ALT; 539 U/L), aspartate transaminase (AST; 518 U/L), total bilirubin (0.4 mg/dl), γ -glutamyl transpeptidase (γ -GTP; 373 U/L), and alkaline phosphatase (ALP; 676 U/L). No signs of viral infection (hepatitis A, B or C, Epstein-Barr, and/or cytomegalovirus), antinuclear or

mitochondrial autoantibodies, or biliary obstruction were present. Our diagnosis was nivolumab-induced Grade 3 hepatic IRAE [6].

The patient was admitted, nivolumab was stopped, and 2 mg/kg/day of intravenous methylprednisolone (IVMP) was started. As the liver injury was refractory to high-dose IVMP, including pulse therapy (figure 1D), coadministration of oral AZA with a maximum dose of 100 mg/day was started (figure 1D). After a month, the liver enzyme levels were normal (AST: 15 U/L; ALT: 30 U/L) and tumour size had increased (figures 1E-G).

The AASLD guidelines for treatment of AIH recommend AZA as the first choice for steroid refractory cases [7], and MMF is considered as an alternative treatment for patients who did not previously tolerate AZA [8-10]. Indeed, there is evidence that AZA-intolerant patients may have higher response rates to MMF than patients refractory to AZA, suggesting that MMF is not always an effective alternative to AZA [8]. Similarly, the evidence that clearly shows the superiority of MMF over AZA in steroid-refractory IRAE is limited [5], despite the recommendation of MMF for steroid-refractory IRAE hepatitis by the manufacturer of nivolumab [4]. Also, the price of MMF at 2 g/day is approximately seven times higher than that of AZA at 100 mg/day. Consequently, we propose that AZA is considered as a legitimate alternative to MMF for steroid-refractory hepatic IRAEs. To the best of our knowledge, this is the first report of a hepatic IRAE successfully managed with AZA. Additional evidence will permit developing an accepted strategy for IRAE management. ■

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1. Raedler LA. Opdivo (Nivolumab): second PD-1 inhibitor receives FDA approval for unresectable or metastatic melanoma. *Am Health Drug Benefits* 2015; 8: 180-3.
2. Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. *Eur J Cancer* 2016; 60: 190-209.
3. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *Eur J Cancer* 2016; 54: 139-48.
4. Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol* 2012; 30: 2691-7.
5. Cheng R, Cooper A, Kench J, et al. Ipilimumab-induced toxicities and the gastroenterologist. *J Gastroenterol Hepatol* 2015; 30: 657-66.
6. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol* 2015; 26: 2375-91.
7. Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010; 51: 2193-213.
8. Hennes EM, Oo YH, Schramm C, et al. Mycophenolate mofetil as second line therapy in autoimmune hepatitis? *Am J Gastroenterol* 2008; 103: 3063-70.

9. Sharzehi K, Huang MA, Schreiber IR, Brown KA. Mycophenolate mofetil for the treatment of autoimmune hepatitis in patients refractory or intolerant to conventional therapy. *Can J Gastroenterol* 2010; 24: 588-92.

10. Gleeson D, Heneghan MA. British Society of G. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. *Gut* 2011; 60: 1611-29.

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IgA-mediated leukaemic vasculitis in a patient with rapid progression of myelodysplastic syndrome to acute myeloid leukaemia

Leukaemic vasculitis is extremely rare in patients with myelodysplastic syndrome (MDS). Although an immunoglobulin (Ig) A-mediated mechanism has been speculated to participate in its pathogenesis, detection of IgA deposition by direct immunofluorescence (IF) has not been so far reported [1]. We describe, herein, a case of leukaemic vasculitis in a patient with MDS and clearly show IgA deposits on vessel walls.

A 79-year-old man presented with multiple erythematous plaques on his trunk and limbs. He had developed fever, arthralgia, and multiple erythematous plaques five days before. Physical examination revealed multiple indurated erythematous plaques on his trunk and limbs (*figures 1A, B*). Laboratory work-up revealed neutropenia (white blood cells: 3,300/ μ L) with no atypical lymphocytes and no differentiation to myeloblasts, slight anaemia (haemoglobin: 10.4 g/dL), thrombopenia (platelets: $11.8 \times 10^4/L$), elevated C-reactive protein (11.87 mg/dL), and slightly elevated serum IgA (518 mg/dL). Anti-proteinase 3 (PR3)-anti-neutrophil cytoplasmic antibody (ANCA) and anti-myeloperoxidase (MPO)-ANCA were negative. Histopathological examination showed a perivascular infiltrate in the dermis and hypodermis (*figure 1C*). Infiltration of atypical mononuclear cells, in addition to a small subset of neutrophils into the vessel walls, was found (*figure 1D*). Fibrin deposition was also found (*figure 1E*). The vessel walls were disrupted (*figure 1F*).

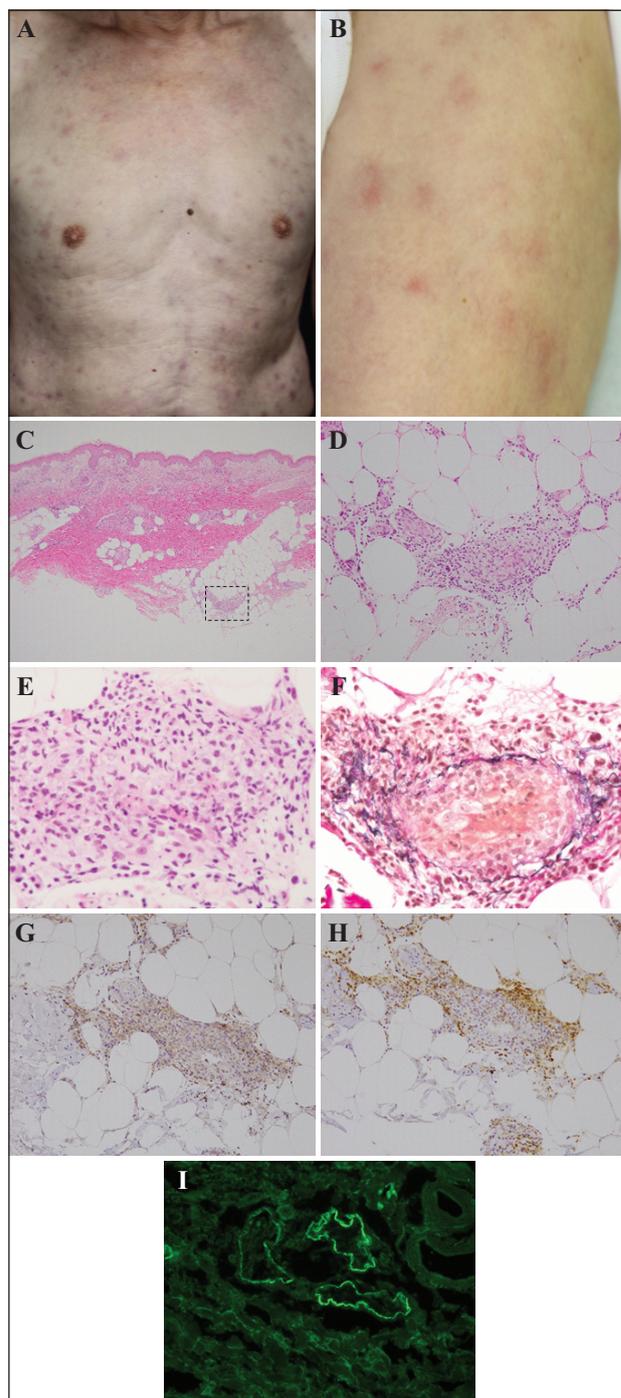


Figure 1. A) Multiple indurated erythematous plaques on the patient's trunk. B) Multiple indurated erythematous plaques on the patient's left forearm. C) Histopathological examination of an erythematous plaque showing a perivascular infiltrate in the dermis and subcutaneous tissue; the dashed box indicates the area shown in (D) (H&E stain; original magnification: $\times 15$). D) Infiltration of atypical mononuclear cells in addition to a smaller subset of neutrophils into vessel walls (H&E stain; original magnification: $\times 200$). E) Fibrin deposition was identified (H&E stain; original magnification: $\times 400$). F) Vessel walls were disrupted (Elastica van Gieson stain; original magnification: $\times 400$). G) Immunohistochemistry for CD33 (original magnification: $\times 200$). H) Immunohistochemistry for MPO (original magnification: $\times 200$). I) Direct IF showing IgA deposition at the vessel walls (original magnification: $\times 200$).

Figure 1.

Immunohistochemical examination revealed that the atypical mononuclear cells expressed CD33 and MPO (*figure 1G, H*). Direct IF revealed IgA deposits on the vessel walls (*figure 1I*). A bone marrow biopsy revealed a focal hypocellular marrow. Karyotypic analysis revealed multiple structural and numerical abnormalities, including a deletion of the long arm of chromosome 5. The diagnosis of MDS (unclassifiable) was made. The histopathological finding that the infiltration of atypical CD33+/MPO+ mononuclear cells disrupted vessel walls may imply a diagnosis of leukaemic vasculitis in MDS because no