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LETTER TO EDITOR

MonoMAC Syndrome Caused by a Novel *GATA2* Mutation Successfully Treated by Allogeneic Hematopoietic Stem Cell Transplantation

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To the Editor:

A 43-year-old woman was referred to the Autoimmune Diseases Unit in 2012 because of anti-nuclear antibody (ANA) positivity detected on Hep2 cells (1:160, homogenous pattern). There was no family history of autoimmune disease, rather a strong family history of colorectal cancer and no parental consanguinity. She had asthma as a child and from age 15 she suffered from guttate psoriasis and hypothyroidism for which she did not receive any systemic immunosuppressive therapy. Vitiligo, in the axillae and thighs, had responded to topical therapy. An atrioventricular nodal re-entrant tachycardia was resolved by radiofrequency catheter ablation. At age 18, a pulmonary mycobacterial infection was refractory to standard therapy requiring right lower lobe resection 18 months later. Histological analysis of the surgical specimen confirmed ongoing parenchymal mycobacterial infection (species unidentified) and she required further therapy.

She was well until age 39 when she complained of fatigue, chronic productive cough, exertional dyspnea, and right-sided pleuritic chest pain. There was no relevant travel history, smoking, occupational, or animal/pet exposure. Further tests revealed reduced diffusing lung capacity, centrilobular micronodularity, and septal and subpleural reticulation with interlobular septal thickening. Bronchial biopsy demonstrated a chronic inflammatory process with erosion and epithelial reactive metaplasia; there were no signs of neoplasia or infection upon bronchial lavage. An open lung biopsy showed multiple bronchiolectasis with areas of suppuration, non-necrotizing granulomas, fibroblast proliferation, pneumocyte hyperplasia, and a mixed inflammatory infiltrate. Acid-fast bacilli, fungal stains, and microorganism cultures obtained from lavage and biopsy specimens, HIV antibody testing, and avian precipitins were negative; serum concentration of alpha 1 antitrypsin, angiotensin-converting enzyme, and vitamin D were in the normal range. Overall findings led to a presumptive diagnosis of hypersensitivity pneumonia. At that time, thrombocytopenia was encountered followed by pancytopenia (Table 1). Of note, there was severe monocytopenia but previous counts were unavailable. Bone marrow aspirate and trephine biopsy were unremarkable.

By the time she was referred to our Autoimmune Diseases Unit, she was followed in Pneumology, Hematology, Gastroenterology, Endocrinology, and Dermatology. Psoriasis was present in the form of erythematous papules (approximately 3 to 5 mm) in the scalp, and extensor surfaces of the arms and thighs. Flow cytometry in whole blood revealed lymphopenia with a total of 695 cells/μL. More specifically, there was a reduced frequency and number of $CD3^+CD4^+$ T cells (28% and 197/μL, respectively; normal range 31–60% and 410–1590 cells/μL), and normal proportion but reduced number of B cells (defined as $CD19^+$; 7% and 47/μL, respectively; normal range 6–25% and 90–660 cells/μL) as well as normal frequency but reduced number of NK cells (defined as $CD3^-/CD16^+56^+$, 11% and 78/μL; normal range 5–27% and 90–590 cells/μL). Immunoglobulin M, G, and A concentrations

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Table 1 Representative peripheral blood counts

Date	2008	2009	2010	2011	2012	2013	2015	2016 (pre-HSCT)	2017 (8 months post-HSCT)	2018 (12 months post-HSCT)
Age (years)	39	40	41	42	43	44	46	47	48	49
Hb (12–15 g/L)	12.4	12.9	11.6	11.5	11.8	11.8	11.8	7.9	11.8	12.2
MCV (78–97 fL)	93.1	92.8	95.9	93	98	94.6	91.9	96.6	95	91
Leucocytes (4500–11,000/μL)	5700	5130	3200	3920	4010	4380	4730	1530	4860	6670
Neutrophils (2000–8500/μL)	4275	2950	1952	2560	2710	3079	3556	994	3090	4750
Eosinophils (0–600/μL)	114	117	64	60	50	91	61	36	40	110
Basophils (0–100/μL)	11	35	0	20	20	22	14	1	0	30
Lymphocytes (900–3500/μL)	1259	1975	1152	1240	1150	1103	1031	390	1070	1170
Monocytes (200–1000/μL)	11	46	32	40	70	83	66	107	660	610
Platelets (150000–400,000/μL)	240,000	159,000	133,000	130,000	89,000	109,000	156,000	61,000	146,000	99,000

*Normal values and units in parenthesis

were normal. Her complex history and presence of pancytopenia with severe monocytopenia suggested GATA binding protein 2 (*GATA2*) deficiency, which was confirmed by targeted next-generation and Sanger sequencing, revealing a 2-bp deletion in exon 4 (c.317_318delCT). This heterozygous mutation was not found in the ExAC Aggregation Consortium (ExAC), the 1000 Genomes (1KG), and the Exome Sequencing Project (ESP) public databases and leads to a frameshift at amino acid 106 (p.S106Cfs) with introduction of a premature stop codon. Although not functionally tested, this novel variant is predicted to cause nonsense-mediated decay of the mutant transcript and to result in *GATA2* haploinsufficiency. At age 45, she was considered for allogeneic HSCT. The bone marrow aspirate and biopsy revealed hypocellularity with multilineage dysplasia and cytogenetic abnormalities: trisomy 8 in the myeloid lineage with a derivative chromosome 1 (ISCN 2016): 47 XX +1, der (1;7) (q10; p10) +8 [9]/46, XX [1], absent from the constitutional karyotype. In the coming years, several events delayed the procedure. Soon afterwards, an incidental unresectable meningioma was diagnosed by magnetic resonance imaging and she underwent stereotactic fractionated radiotherapy (total dose of 54 Gy using 1.8 Gy/fraction). Epstein-Barr virus serology and blood PCR were negative. She also developed erythema nodosum. Lesions caused by human papillomavirus (HPV) were resected from the vaginal wall, sigmoid colon, and anorectal transition. The revised histological report from the lung biopsy was now compatible with alveolar proteinosis.

At age 48, she underwent a T cell replete peripheral blood HSCT containing 6.45×10^6 $CD34^+$ cells/kg and 21.4×10^7 $CD3^+$ T cells/kg. The donor was a human leukocyte antigen–identical sibling who tested negative for the identified *GATA2* mutation. Cytomegalovirus (CMV) serostatus was positive for both donor and recipient. She was subjected to a reduced-toxicity conditioning regimen with fludarabine 160 mg/m^2 (days − 6 to − 3) and busulfan 12.8 mg/kg (AUC adjusted days − 6 to − 3). Tacrolimus and mini-dose methotrexate were used for graft versus host disease (GVHD) prophylaxis in addition to prophylactic acyclovir, posaconazole, isoniazid, and ciprofloxacin. Engraftment date was recorded on day + 11 (> 500 PMN) and she was discharged 21 days after the transplant. Short tandem repeats provided information regarding the chimeric status of the patient (> 95% sample purity): one month post-HSCT, recipient marrow revealed myeloid (CD33), lymphoid (CD3), and stem cell (CD34) chimerism of 100%, 67%, and 100%, of donor origin, respectively. In turn, nine months later, peripheral blood revealed an increase of donor myeloid and lymphoid cells to 100% and 89%. A short reactivation of CMV infection was treated uneventfully with intravenous ganciclovir. Tacrolimus was adjusted to regular serum drug concentration monitoring and suspended after nine months. In the following two months, she developed a moderate form of chronic GVHD with cutaneous and gastrointestinal tract involvement, responding to an

intermediate steroid dose and cyclosporine. Her main features pre- and post-HSCT are presented in Supplementary Fig. 1. There has been full hematological reconstitution (Table 1) with symptomatic and functional pulmonary improvement. More specifically, pre-HSCT DLCOc/VA (mmol/min/kPa/L) increased from 1.27 (76.1% of expected) to 1.34 (80.9% of expected), at one year post-HSCT. Repeat cerebral MRI shows an identical tumor size. At 12 months after HSCT, the patient has no recurrent infections and presents normal cell counts with a Karnofsky performance status of 90%. There was full clearing of psoriatic lesions after HSCT.

GATA2 mutations can manifest in a heterogeneous fashion predominantly affecting the bone marrow, the lung, and the skin associated to a spectrum of immunodeficiency, severe infections, and myeloid neoplasms [1]. The patient is likely to have suffered from an atypical mycobacterial infection in addition to alveolar proteinosis, HPV infection, erythema nodosum, progressive pancytopenia (with severe monocytopenia), irregular lymphocyte phenotyping (mild reduction in $CD4^+$ T, B, and NK cells), and bone marrow cytogenetic abnormalities, all of which are characteristic of the MonoMAC syndrome. Despite the fact that the patient presented with a novel mutation, its association to her clinical features remains speculative. Poorly characterized autoimmune features have been heralded as a feature of MonoMAC but in fact only very few patients present with bona fide autoimmune diseases [2]. In addition, to our knowledge, this is the first time a meningioma has been described in MonoMAC syndrome. NK cell deficiency may theoretically lower tumor surveillance, but it was not a significant finding in the patient. In agreement with the strong family history of colorectal cancer, the possibility remains that she may harbor other somatic mutations.

Despite a long diagnostic delay and a complicated post-transplant trajectory, the patient benefited from HSCT as described in recent reports [3, 4]. *GATA2* mutations have been previously diagnosed in two young Portuguese siblings who died [5]. It is important for clinicians worldwide to become more familiar with this potentially lethal primary immunodeficiency syndrome manifesting in adulthood.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Patient signed informed consent for genetic analysis and case publication.

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