CASE REPORT

MonoMac syndrome with associated neurological deficits and longitudinally extensive cord lesion

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SUMMARY

We present a case of monocytopenia and mycobacteria-related infection (MonoMac) syndrome in a 30-year-old man of Indian origin. The clinical diagnosis of *GATA2* haploinsufficiency was suspected after an unusual neurological presentation on a background of myelodysplastic syndrome and childhood pulmonary tuberculosis. The patient had a longitudinally extensive spinal cord lesion and a lesion in the medulla. No obvious infective cause for the spinal cord MRI abnormality was found, and the lesions were presumed to be inflammatory in nature. The family history consisted of autosomal dominant clinical features suggestive of *GATA2* haploinsufficiency. Genetic testing in peripheral leucocytes revealed a pathogenic mutation in *GATA2*. This is the first-ever published case of possible MonoMac syndrome with a neurological presentation. The case highlights the rarity and complexity of the diagnosis and the clinical sequelae that ensued with the patient dying of gram-negative septicaemia while receiving intravenous steroid therapy for the spinal cord lesion.

BACKGROUND

Monocytopenia and mycobacteria-related infection (MonoMac) syndrome is caused by mutations in the gene *GATA2*.¹ *GATA2* codes for a transcription factor important in the regulation of haemopoiesis which when mutated results in absent to abnormally low levels of monocytes, dendritic cells, natural killer (NK) cells and B cells.^{1,2} The syndrome is associated with immunodeficiency, opportunistic infections and haematological malignancy.^{1,2} Patients typically present in early adulthood with recurrent non-tuberculous mycobacterial infection, myelodysplastic syndrome, disseminated warts (papilloma virus infections), opportunistic fungal infections or pulmonary alveolar proteinosis.¹ Bone marrow failure can be treated with blood or platelet transfusions or bone marrow transplant. Here, we present an interesting case of a 30-year-old man of Indian origin whose clinical diagnosis of *GATA2* insufficiency was suspected after an unusual neurological presentation with lower limb neurological deficits and urinary retention on a background of possible myelodysplastic syndrome and childhood pulmonary tuberculosis. He had an autosomal dominant family history of features suggestive of *GATA2* haploinsufficiency. Genetic testing in peripheral leucocytes revealed a pathogenic mutation in *GATA2*. As he died from the opportunistic infection before an alternative tissue

sample could be obtained, it remains unestablished if this mutation was somatic or present in his germline. MonoMac syndrome is rare, but it can have devastating consequences. Hence a high degree of suspicion by neurologists, haematologists and infectious diseases specialists is required for its diagnosis.

CASE PRESENTATION

A 30-year-old man of Indian origin was referred to the neurology outpatient clinic with a 1-year history of paraesthesia in his lower limbs and intermittent urinary retention. He also described L'hermitte's phenomenon. There was a history of urinary hesitancy for the last 2 months, with intermittent urinary retention. He denied weakness in his arms or legs. He also reported intermittent lower back pain for several months. He denied any fevers or history of rigours. He denied any rashes. He denied constipation or diarrhoea. He had lost 15 kg of weight unintentionally over the last 2 years but his appetite remained normal. His close contacts had been well recently.

His medical history included tuberculosis (TB) diagnosed at the age of 10 and treated for the subsequent 12 months. His other history was significant for 'congenital bone marrow failure'/'early myelodysplasia'. Abnormal blood cell parameters were noted initially when the patient was 10 years old but were said to have subsequently normalised. In 2013, while being investigated for a several month history of lethargy, he was noted to have low blood counts, and after a bone marrow aspirate, he was given a diagnosis of possible early myelodysplasia (MDS). He was transfusion dependent from 2013 to 2015 because of symptomatic anaemia. Routine cytogenetic tests were normal, and he had been considered for an allogeneic stem cell transplant in the future if there was disease progression.

The patient also reported a background history of recurrent molluscum infection ('warts') on his hands and fingertips, scrotal calcinosis as well as acne vulgaris. Also, there was a history of recurrent chest infections in his childhood. The last severe case of pneumonia he had was 5 years prior. He had previously been given a diagnosis of asthma with a forced expiratory volume in one second (FEV₁)/forced vital capacity of 63% and FEV₁ of 2.3 L with correction postbronchodilator. A diffusing capacity of the lungs for carbon monoxide was found to be slightly reduced, and the possibility of pulmonary parenchymal disease was also entertained. His other medical history was significant for subclinical hypothyroidism.

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Figure 1 Pedigree showing the patient (proband) and his immediate family members. His sister had deceased in her 20s due to thrombocytopaenia-related complications (bleeding) and his brother had deceased also in his 20s due to leucopenia-related complications (mycobacterial infection of the oesophagus). The patient's father had deceased from an asthma/COPD-related illness. COPD, chronic obstructive pulmonary disease; LL, lower limb; TB, tuberculosis; y, year.

His medications at the time of presentation to neurology outpatients included: deferasirox 250mg in the morning and 500mg in the night for iron chelation in the setting of monthly blood transfusions, fluconazole 200mg in the night, valaciclovir 500mg in the night, thyroxine 50 µg Monday to Friday, 100 µg on Saturday and Sunday, diphenylcyclopropenone 0.25% and salicylic acid 15% topical in the night (for warts), Boroline antiseptic cream as needed and zinc tablets (50mg) in the night (for acne). He had an allergy to penicillin (rash).

The patient was born in India and migrated to Australia in 2013 after marriage. He had no children. He worked full time in information technology. He denied ethanol intake and there was no history of cigarette smoking. There was no history of illicit substance abuse. Two of his siblings had deceased in their 20s from cytopaenia-related complications (figure 1). His parents were not consanguineous and his father had deceased from asthma/chronic obstructive pulmonary disease-related complications. The patient had a step brother who was well.

On examination, the patient had no dysmorphic features. He was of normal stature. He did not have any radial ray defects, café-au-lait macules or abnormal skin pigmentation. There was evidence of previous molluscum infection on his fingertips on both hands. His nails were normal with no evidence of dystrophic changes. He had scrotal calcinosis. Cardiovascular and respiratory examination was normal. He was afebrile and his blood pressure was 100/60mm Hg. There was no cervical or axillary lymphadenopathy. His thyroid exam was normal, with no palpable nodules. There was no hepatomegaly. He had mild splenomegaly. Visual acuity was 6/6–2 bilaterally (uncorrected). His visual fields and extraocular eye movements were normal. There was no diplopia. There was no nystagmus. Funduscopic examination was normal with no evidence of papilloedema or disc pallor. Neck flexion elicited a L'hermitte's symptom. Upper limb examination revealed normal tone and power bilaterally,

but the tendon reflexes were increased symmetrically (+++). There was no finger nose dysmetria. Sensation to pin prick and vibration sense were intact. He had a normal gait and there was no heel toe ataxia. His lower limb neurological examination revealed increased tone with five beats of clonus bilaterally. The power was normal in the lower limbs. The tendon reflexes were brisk (+++) throughout. The plantars were normal and down going. There was a sensory (pin prick) level up to T10 bilaterally.

INVESTIGATIONS

Investigations revealed a haemoglobin of 94g/L with white cells of $2 \times 10^9/L$, neutrophils of $0.9 \times 10^9/L$, platelets of $61 \times 10^9/L$, monocytes of $0 \times 10^9/L$ (normal range: 0.20–1.00), lymphocytes of $0.4 \times 10^9/L$ (consisting of CD4: 0.25 (0.35–2.63), CD3: 0.39 (0.7.3.58), CD8: 0.18 (normal), CD19: 0 (0.05–0.89)). The creatinine, urea and electrolytes including calcium, magnesium and phosphate were normal. He had normal thyroid function tests without elevation in routinely tested thyroid antibodies. His liver function tests were normal apart from hyperbilirubinaemia of 30 µmol/L (unconjugated) which was long-standing.

Hepatitis B, hepatitis C and HIV serology were negative. The cytomegalovirus (CMV) and Epstein-Barr virus (EBV) serology were suggestive of previous CMV and EBV infection. Toxoplasma serum IgM antibody was not detected. Quantiferon gold testing for TB was negative. Bacterial blood cultures were negative. Copper and zinc levels were normal, and there was no evidence of vitamin B₁₂ deficiency. Serum folate was also normal. Antinuclear antibody (ANA), double-stranded DNA, extractable nuclear antibody were all negative. Antineutrophil cytoplasmic antibodies including proteinase 3 were negative. Perinuclear ANCA with myeloperoxidase were also negative. The erythrocyte sedimentation ratio was 20mm/hour (normal range 0–25), with a C reactive protein of 16mg/L (normal

Figure 2 (A) Coronal and (B) sagittal images showing a large T2 and FLAIR hyperintense lesion in the ventral aspect of the medulla oblongata involving primarily the medullary pyramids and to lesser extent the olives. (C) The conus and the inferior aspect of the thoracic spinal cord are mildly expanded with abnormal T2 hyperintensity posteriorly extending for approximately 5 cm superiorly (from lower T12 endplate level to upper T11 endplate level). This abnormality is associated with a midline dorsal focal cord enhancement at T11/12 measuring approximately 6×4×4 mm. Arrows indicate the T2 signal change. FLAIR, fluid-attenuated inversion recovery.

range 0–5). His complement levels were slightly reduced with a C3 of 0.76 g/L (normal range 0.82–1.85) and C4 of 0.13 g/L (normal range 0.15–0.53). Immunoglobulin levels were normal, without evidence of specific antibody deficiency. Serum ACE was not elevated. Schistosomiasis serology and PCR for the John Cunningham virus were negative.

A bone marrow aspirate was variably cellular with evidence of erythroid hyperplasia and dyserythropoiesis. There was reduced granulopoiesis and evidence of borderline dysplasia in megakaryocytes. Chromosomal instability studies were negative for Fanconi anaemia. Telomere length testing for dyskeratosis congenita was normal. The overall impression was that the findings were suggestive of ‘congenital marrow failure’ with possible early MDS.

A CT of the abdomen, chest and pelvis showed no evidence of malignancy. In the chest, there were right upper lobe changes consistent with the history of TB. An MRI of the lumbar and lower thoracic region 3 months previously had shown abnormal T2 signal in the conus region. There was also diffusely abnormal bone marrow signal relating to the underlying haemopoietic disorder. Repeat MRI scan revealed that the conus and the inferior aspect of the thoracic spinal cord were mildly expanded with abnormal T2 hyperintensity posteriorly extending for approximately 5 cm superiorly (from the lower T12 endplate level to upper T11 endplate level) (figure 2). This abnormality was associated with a midline dorsal focal cord enhancement at T11/12 measuring approximately 6×4×4 mm. There was no other signal change apparent in either the cervical or thoracic spinal cord at this stage. The spinal canal was patent with no compromise to nerve roots observed at the exit foraminae. No vascular abnormality was identified. The differential diagnosis was posited to include inflammatory/infective myelitis and central demyelination.

An MRI of brain showed a confluent relatively large T2 and fluid-attenuated inversion recovery (FLAIR) hyperintense lesion in the ventral aspect of the medulla oblongata involving primarily the medullary pyramids and to lesser extent the olives (figure 2). There was no definite lesion in the pons or the midbrain. There were multiple small T2 lesions in the cerebral white matter, but not in a distribution characteristic of multiple sclerosis (MS).

The antiaquaporin 4, anti-Yo, anti-Ri and anti-Hu antibodies were not detected. Vitamin E level was normal. A Wilson’s disease screen was also negative.

A cerebrospinal fluid (CSF) analysis revealed 5×10^6 /L erythrocytes, 2×10^6 /L lymphocytes, 0×10^6 /L polymorphs, a glucose of 3.1 mmol/L and a mildly elevated protein of 0.51 g/L. Herpes multiplex PCR and human T-cell lymphotropic virus type 1 (HTLV) PCR were negative. Oligoclonal bands were positive in the serum and CSF. Staining for acid fast bacilli (AFB) on CSF was negative. Culture for TB and TB PCR performed on the CSF were also negative.

A repeat MRI scan 3 months subsequently revealed a stable appearance of the T2 hyperintense lesions in the brain. There was interval development of a midline dorsal T2 hyperintensity without enhancement in the cervical spinal cord extending from the C2 to C4/C5 intervertebral disc levels. The lesion in the lower thoracic cord had significantly improved. During the interval between the two MRI scans, the patient had not received any steroids or other immunotherapy.

Chromosome microarray revealed male molecular karyotype with no copy number variation. Targeted GATA2 DNA sequencing and multiple ligation-dependent probe amplification on peripheral blood sample showed heterozygous deletion in GATA2 as described below:

GATA2:c.1018-?_*+del (exons 5–6 inclusive) p.(?)

This variant is not listed in the Human Gene Mutation Database (2015.2) or GATA2 lsdb. It affects the Zinc finger 1 and 2 domains and the nuclear localisation signal. An extensive literature review has not revealed any previous report of this deletion. This deletion is predicted to cause deletion of the C-terminal region of the GATA binding protein 2 structure and function and therefore is likely pathogenic. No other mutations were detected.

However, given that the patient had possible MDS, these results cannot determine if the GATA2 deletion is germline or somatic. Normally, a hair bulb or skin sample would be tested to confirm this, but as the patient had died soon after the genetic testing was organised, this remains unestablished.

DIFFERENTIAL DIAGNOSIS

This is the first reported case of MonoMac Syndrome with neurological deficits and cord lesions. Differential diagnoses that were considered included TB myelopathy and HTLV-associated myelopathy. In TB myelopathy, the spinal cord may be affected in different ways in the course of tuberculous infection. A

retrospective study over a 7-year period in a tertiary hospital in Iran found 43 cases of tuberculous myelopathy.³ Manifestations included backache (86%) and fever (67%).³ Twenty patients were paraparetic or paraplegic. Our patient did not report any fever, and fever was only evident in the 2 days leading up to his death when he had developed *Escherichia coli* bacteraemia. Also, all investigations for active TB including CSF AFB stain, TB PCR and TB culture were negative making this diagnosis unlikely.

HTLV-associated myelopathy is caused by the HTLV-1. It can lead to slowly progressive spastic paraparesis and urinary disturbance.⁴ It is usually associated with thoracic cord signal abnormalities with inflammation of cord but with sparing of the posterior columns.^{4,5} MRI generally shows spinal cord atrophy, particularly of the thoracic cord.^{4,5} A brain MRI often shows subcortical, periventricular white matter lesions.⁴ The CSF can reveal a mild lymphocytosis and/or elevated protein concentration in some patients.⁴ Anti-HTLV-I antibodies are detected in the CSF with a high CSF/serum ratio.⁴ Steroids and other immunomodulatory treatment may slow progression, but this is not proven.⁶ Importantly, our patient's CSF PCR was negative for the HTLV-1 virus.

Conditions such as MS and neuromyelitis optica (NMO) were also considered. However, the MRI findings were not typical of MS and given oligoclonal bands were positive in CSF and serum the specificity for MS was low. Also, the history did not fit that of MS or its variants. In regards to NMO, aquaporin 4 antibody was negative. Anti-myelin oligodendrocyte protein (MOG) antibody was not tested, but given the diagnosis of early MDS and dominant family history of cytopenia, the consensus was that an NMO spectrum (astrocytopathy) or an MOG antibody positive (oligodendrogliopathy) disorder was unlikely. In the context of the MonoMac syndrome, it is possible that the cord lesions were the result of a non-TB mycobacterial infection, but this was not formally assessed because of the difficulty and risks of biopsy directed to the spinal cord.

OUTCOME AND FOLLOW-UP

The patient's neurological condition subsequently deteriorated with worsening lower limb symptoms with now associated sensation of heaviness in his legs and difficulty ambulating. His urinary retention was also getting worse. Investigations for TB were negative. Testing of CSF for TB and TB-related bacilli was negative. Given his worsening neurology, he was given 500 mg of intravenous methylprednisolone. There was some improvement in his clinical state with administration of methylprednisolone. Unfortunately in the setting of long-standing pancytopenia, he developed gram negative (*E. coli*) septicaemia requiring inotropic support, but he died as a result of multiorgan failure and sepsis. Genetic testing performed prior to the patient's death subsequently revealed a mutation in the GATA2 transcription factor.

DISCUSSION

We present a case of a 30-year-old man from India with history of active TB at the age of 10 and long-standing issues of pancytopenia and dominant family history of cytopenia and cytopenia-related complications. The patient had presented with lower limb paraesthesia and a sensory level of T10 with urinary retention. There were extensive T2 and FLAIR hyperintensities on MRI in the distal thoracic and proximal lumbar cord. These MRI changes were dynamic in character, in that they had largely resolved on repeat MRI 3 months later, but by this stage the patient had developed a new cervical T2 hyperintense lesion. This case is likely to be one of MonoMac syndrome and highlights the

complexities of treating a patient with extensive T2 and FLAIR cord signal abnormalities with worsening neurology in setting of pancytopenia and risk of sepsis.

MonoMac syndrome is a syndrome of monocytopenia associated with non-TB mycobacterial infection and other opportunistic infections.¹ The case reported certainly had a previous confirmed diagnosis of TB as a child and a history of subsequent bacterial and viral chest infections. There was however no confirmed diagnosis of non-TB mycobacterial infection in the patient. The patients with MonoMac syndrome are prone to recurrent viral and fungal infections,^{1,7} and this was evident in our patient by his long-standing history of recurrent molluscum infections (warts). MonoMac syndrome is associated with increased incidence of myelodysplasia,^{1,8,9} and our patient's bone marrow was suggestive of this. MonoMac syndrome is inherited in an autosomal dominant manner,⁷ and our patient's family history of pancytopenia certainly fitted this pattern of inheritance. Often the individuals with MonoMac syndrome have a first-degree relative with history of opportunistic infections and MDS,¹ and this was noted in our case. The syndrome and its complications are usually observed in adulthood. The individuals with MonoMac syndrome have persistent monocytopenia and NK lymphopenia as a characteristic feature,² and this patient had non-existent levels of monocytes. Low CD4, CD8 counts and neutropenia are also seen.² Immunoglobulin levels are generally normal in MonoMac syndrome and we did not observe any abnormalities in this regard in the reported case. The syndrome of MonoMac is associated with GATA2 mutation, and this was confirmed on peripheral blood leucocyte genetic testing performed prior to the patient's death.

GATA is a member of a family of transcription factors containing zinc fingers in their DNA binding domain. They are candidate regulators of gene expression in haematopoietic cells.⁷ GATA2 is thought to regulate monocyte, macrophage, dendritic cell, B-cell and NK-cell ontogeny and function, as well as the susceptibility to develop MDS and Acute Myeloid Leukaemia (AML).¹⁸ Although we were unable to obtain specimens from the patient's immediate relatives for genetic testing, given the strong family history of cytopenia and cytopenia-related complications, we

Learning points

- ▶ Monocytopenia and mycobacteria-related infection (MonoMac) syndrome is a rare genetic condition with mutation in GATA2 transcription factor.
- ▶ It can manifest with cytopenia and mycobacterial infections.
- ▶ We present the first-ever case of MonoMac syndrome with a GATA2 mutation where the patient presented with neurological symptoms and associated longitudinally extensive spinal cord lesion.
- ▶ A learning point from this case was that MonoMac syndrome could potentially present with neurological signs and symptoms and one needs to use caution in treating the underlying neurology, as the myelopathy/spinal cord signal may not be simply demyelination.
- ▶ Infection also needs to be considered.
- ▶ This case highlights the need for neurologists, haematologists and infectious disease specialists to be very vigilant in identification of MonoMac syndrome and to be aware of the cytopenia-related complications that can lead to high morbidity and mortality.

presume the patient's siblings who are also deceased suffered from the same syndrome.

Both autosomal dominant and sporadic cases of MonoMac/GATA2 mutation have been reported.^{1 2} Given multiple family members were affected with pancytopenia, we presume that the mutation our patient carried is one of germline dominant transmission and not sporadic. Successful non-myeloablative haematopoietic stem cell transplantation has been reported in several cases of GATA2 deficiency, and this resulted in reconstitution of the severely deficient monocyte, B-cell and NK-cell populations and reversal of the clinical phenotype.¹⁰ Our patient unfortunately deceased from gram-negative sepsis and multiorgan failure. Given the high morbidity and mortality associated with MonoMac syndrome, the ability to identify those at risk and screen for GATA2 mutation remains critical.

Contributors MM, TK and LC were the clinicians involved in patient's care. MM and TK were involved in conducting the neurological assessment and investigations as well as postulating on the diagnosis of MonoMac syndrome. LC was the patient's haematologist and was responsible for conducting the haematological investigations and their interpretation. AH was responsible in seeing the patient in genetics clinic and assessing the patient for consideration of GATA2 mutation. The report was written by MM with edits performed by the other authors.

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