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CASE REPORT

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Many signs, one mutation: Early onset of de novo GATA2 deficiency syndrome. A case report

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ABSTRACT

We report a case with a broad spectrum of symptoms, related to GATA2 deficiency syndrome, which emerged as early as at 6 months of age. They ranged from lymphedema, deafness to myelodysplastic syndrome (MDS).

KEYWORDS

deafness, GATA2, lymphedema, myelodysplastic syndrome, warts

1 | INTRODUCTION

Myelodysplastic syndrome (MDS) is a rare disease of childhood, with a 0.8 to 1.8 per million children estimated frequency[1] and its diagnosis should include the investigation of a bone marrow failure syndrome (BMFS) or a familial form caused by GATA2 deficiency.

GATA2 mutations were identified as a significant MDS/AML genetic predisposition in 2011.[2] Germline *GATA2* mutations account for 7% of primary childhood MDS[3] being the most commonly known genetic cause. These mutations not only are linked to bone marrow failure (BMF), MDS, or acute myeloid leukemia (familial MDS/AML),[2] but these patients can also show immune alterations with monocyte, B- and natural killer (NK)-cell deficiency, such as MonoMAC [4] or dendritic cell, monocyte, and B- and NK-lymphoid deficiency (DCML) syndromes.[5]

Emberger or deafness-lymphedema-leukemia syndrome is a very rare, autosomal-dominant, genetic disorder with a prevalence of <1/1 000 000.[6] It is characterized by primary lymphedema, immunodeficiency, and MDS/AML.

2 | CASE REPORT

We report the case of an 18-year-old male patient who developed right leg lymphedema at the age of 6 months, which improved with ambulation. He was diagnosed with bilateral sensorineural deafness at 3 years of age and started language acquisition after cochlear implant surgery. At the age of 7,

right hand finger warts appeared, followed by a lower lip wart one year later. It was removed by cryosurgery. By that same age, he was diagnosed with atopic dermatitis. At the age of 8, low neutrophil (0.92-1.8 × 10^9/L) and monocyte (0.01-0.02 × 10^9/L) counts were noticed. IgG and IgM anti-neutrophil antibodies were detected. B-cell lymphopenia (4%) with a CD4/CD8 inversion was also found.

New lower lip warts developed at 15 and 16 years of age, requiring further cryosurgery. At 13 years, right toe cellulitis developed following trauma, with apparent resolution after oral antibiotics. However, two weeks later, hospitalization was needed due to right leg erythema, fever, and serum C-reactive protein levels above 320 mg/L. Intravenous amoxicillin-clavulanic was delivered, and surgical toenail removal had to be performed. Ten more cellulitis episodes were recorded in the next 5 years, four of them requiring admission to the hospital. All the cellulitis events were caused by methicillin-sensitive *Staphylococcus aureus*. Seven further toenail removals had to be undertaken. Right limb lymphedema (Figure 1E) relapsed after the first hospitalization. An indocyanine green fluorescent lymphangiography at 15 years of age confirmed the absence of right leg active lymphatic vessels. Therefore, lymphatic venous anastomosis could not be performed, and conservative care with compressive garment and physiotherapy was implemented.

The patient developed acne at 12 years, and he received various treatments over the years. At 20, it evolved into a papule pustulous form, and the patient is now on isotretinoin PO and topic tacrolimus.

At 14 years, mild anemia (hemoglobin 111 g/L) emerged, followed by thrombocytopenia (116 x 10^9/l). Three years later, dysmorphic red blood cells were noticed in the peripheral blood smear. Bone marrow biopsy showed a markedly hypocellular marrow with atypical megakaryocytes (large forms with separated nuclear lobes). Bone marrow aspirate assessment showed degranulated and hypolobated neutrophils (88%) and dysplastic erythropoiesis (40%), with no increase in the blast cell count (Figure 1A-D), fulfilling criteria for myelodysplastic syndrome with multilineage dysplasia. The cytogenetic assessment showed a normal karyotype. Next-generation sequencing with a molecular custom panel identified a previously reported pathogenic mutation at *GATA2* gene c.1084C > T; p.R362*. These findings were confirmed by Sanger sequencing. Therefore, the patient was diagnosed with myeloid neoplasm with germline *GATA2* mutation, which is listed within the myeloid neoplasms with germline predisposition associated with other organ dysfunction in the WHO 2017 Classification.[7] Family history was unremarkable for infection susceptibility, solid, or hematologic malignancies. His parents were born in Morocco, and they showed no known consanguinity. The parents, as well as his older sibling, tested negative for the *GATA2* gene c.1084C > T; p.R362* mutation.

After establishing the diagnosis mentioned above, a closer follow-up with biannual blood tests and physical examination were established. A matched related donor (MRD) search was unsuccessful, and a matched unrelated donor (MUD) search is being carried out.

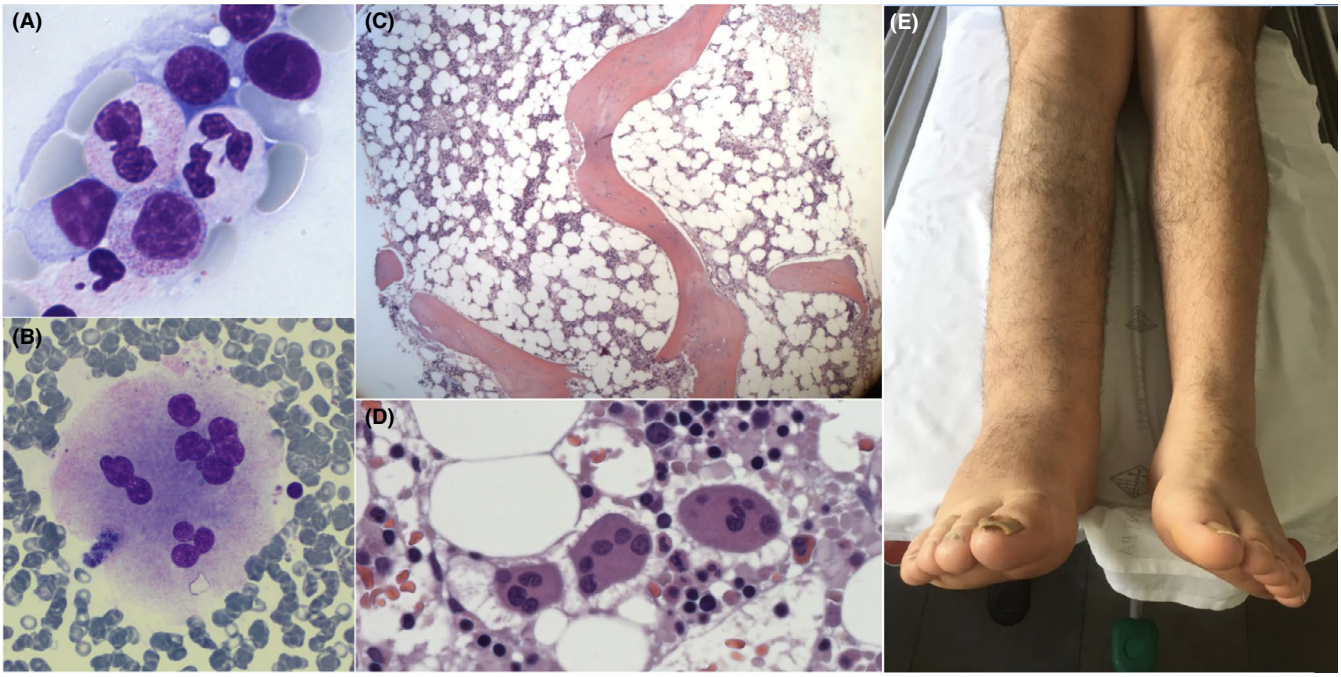


FIGURE 1 A, Degranulated neutrophil. B and D, Atypical megakaryocytes. C, Bone marrow section showing hypocellularity. E) Right lower extremity lymphedema

The patient is in good clinical condition at present, and his blood cell counts have remained stable for the last six years (hemoglobin 101-125 g/L, platelets 75-134 × 10^9/L, neutrophils 0.75 × 10^9/L, monocytes 0-0. × 10^9/L, and lymphocytes 0.44-1.54 × 10^9/L). The last hospitalization for cellulitis took place two years ago, and the last skin infection event, one year ago. He is a computer science student and carries out an independent life.

3 | DISCUSSION

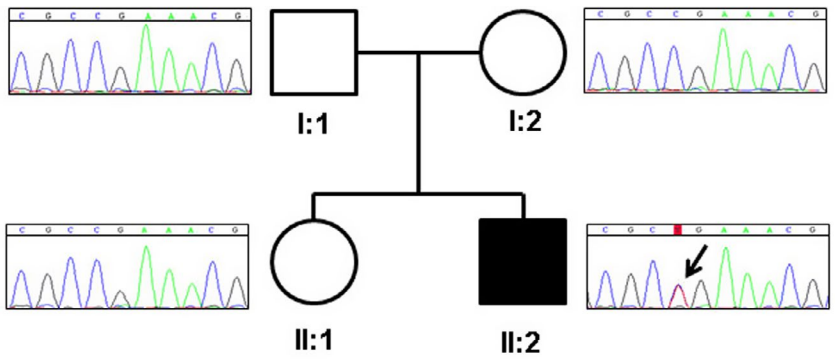
GATA2 deficiency caused by inactivating mutations may give rise to a disorder with multiple clinical manifestations. Hematologic malignancy is a relevant and common feature (>80%) [3,8-10] and may develop without any other symptoms. In the largest series reported,[3,8-10] infections were the second in frequency—mostly viral [8]—followed by pulmonary alveolar proteinosis (PAP), HPV-related dysplasia, chronic lymphedema, venous thrombosis, sensorineural hearing loss, miscarriage, hypothyroidism, and autoimmune phenomena.

In this report, we describe a GATA2 deficiency case showing Emberger syndrome features that emerged as early as the age of 6 months old as lymphedema and deafness at three years old. Hematologic manifestations appeared later. Neutropenia, along with monocytopenia and low B-lymphocyte count, was first noticed at eight years of age and followed by anemia and thrombocytopenia nine years later.

A known pathogenic nonsense mutation c.1084C > T in the ZNF2 domain (exon 5) was detected on NGS analysis and confirmed by Sanger sequencing. The patient also harbored a nonpathogenic variant allele at *GATA2* (c.490G > A), shared by his parents and sister, which were all healthy and tested negative for the pathogenic *GATA2* mutation both by NSG and Sanger sequencing (Figure 2). These findings imply that the *GATA2* mutation was de novo.

More than 100 *GATA2* mutations have been reported to date.[11] Approximately one-third of germline mutations are inherited while the rest occur, as in our case, de novo.[3,12] Pathogenic germline variants comprise three main types: 45% missense or indel mutations within ZF2; 40% truncating (nonsense, indels, and splice site changes) mutations preceding or within ZF2; and 10% belong to noncoding variants in intron 4 which alter the + 9.5 kb regulatory site. Much less common (around 5%) are complete gene deletions or frameshift and nonsense mutations scattered along the gene, and missense mutations C-terminal of ZF2.[12,13] Pathogenic variants seem to induce haploinsufficiency by different mechanisms. These include hemizygosity due to loss or reduced transcription of one allele or truncation of GATA2 protein and the resulting reduced or abolished function.[12] This, in turn, could cause decreased DNA-binding capability and transactivation alterations.[14] Moreover, protein changes can cause loss of *GATA2* autoregulation [15]

A study of a pedigree with the recurrent p.T354M gave some insight into epigenetic control and allelic balance between the WT and mutated allele.[16]



	Gene	Depth	VAF	cDNA mutation	Protein mutation
I:1	TET2 EZH2	7206 6137	99.8 50.1	c.5284A>G c.637C>T	p.Ile1762Val p.Arg213CYs
I:2	GATA2 TET2	4142 5480	99.5 50	c.490G>A c.652G>A	p.Ala164Thr p.Val218Met
II:1	TET2 EZH2 GATA2 TET2	5842 4780 5602 5869	49.5 49.7 49.4 51.2	c.5284A>G c.637C>T c.490G>A c.652G>A	p.Ile1762Val p.Arg213CYs p.Ala164Thr p.Val218Met
II:2	**GATA2** GATA2 TET2 EZH2	**3959** 3981 4100 3712	**48.3** 50.6 49.4 47.3	**c.1084C>T** c.490G>A c.5284A>G c.637C>T	**p.Arg362*** p.Ala164Thr p.Ile1762Val p.Arg213CYs

FIGURE 2 *GATA2* Sanger sequencing for the patient and his family (top). NGS findings are also shown (bottom)

High levels of GATA2 protein have been found in lymphatic vessels of embryonic and adult mice, especially in leaflets from vascular valves.[17] Oscillating shear stress can induce GATA2, and it binds to a –11 kb *PROX1* enhancer, resulting in its transactivation.[18] Investigation of the three most prevalent *GATA2* missense mutations [14] showed a genotype-phenotype correlation where *GATA2* mutants with residual activity in terms of DNA-binding capability did not develop lymphedema. Therefore, GATA2 haploinsufficiency resulting from a null mutation may combine with either inflammation or infections to trigger lymphedema onset,[18] as in our case.

Given the various mutational spectrum of *GATA2*, a negative NGS panel in the context of clinical suspicion cannot rule out a GATA2 deficiency syndrome. In some cases, whole gene deletions or intronic mutations may be missed when testing only for coding exons. In patients with immunodeficiency, recurrent infections and somatic features, or an MDS diagnosis at a young age, it is mandatory to screen for germline mutations. This approach should include analysis of intron 4 of *GATA2* and MLPA or DNA arrays to search for large chromosomal deletions encompassing *GATA2*.

Once a GATA2 deficiency syndrome diagnosis is established, a thorough family history should be undertaken.

Patients diagnosed with GATA2 deficiency syndrome should undergo close follow-up. Hematopoietic stem cell transplantation is the treatment option of choice, and MRD or URD seems to offer better outcomes than cord blood.[19] HSCT optimal timing has not been clearly established. However, the development of MDS, severe infections, or pulmonary complications is considered HSCT indications. Concerning MDS, it seems advisable to proceed to HSCT when in hypocellular stage, before the phase of increasing numbers of bone marrow blasts.[19] Our patient had not developed complications such as PAP or life-threatening infections, being MDS his only HSCT indication to date. Unfortunately, Emberger syndrome patients who underwent HSCT did not experience lymphedema reversal.[20,21]

4 | CONCLUSION

We report a case with a broad spectrum of symptoms, related to GATA2 deficiency syndrome, which emerged as early as at six months of age. They ranged from lymphedema, deafness, which is one of the less frequently described features, to myelodysplastic syndrome (MDS), which is a highly penetrant phenotype within this syndrome. It also included recurrent infections, although they were not life-threatening. Our case illustrates the clinical manifestations associated with loss of function *GATA2* mutations and how all of these may precede MDS diagnosis.

ETHICAL APPROVAL STATEMENT

Photographies were obtained with written informed permission.

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Published with written consent of the patient.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

MLB: has made substantial contributions to conception, design, and analysis and interpretation of data, and wrote the manuscript; MT and IB cared for the patient and made contributions to the paper; EB: performed molecular analysis; JFN: was involved in the design and interpretation of data, wrote and review the manuscript.

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