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Skin manifestations among GATA2-deficient patients

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ABSTRACT:

GATA2 mutations have been identified in various diseases, such as monoMAC syndrome, Emberger syndrome, familial myelodysplastic syndrome, acute myeloid leukemia, and dendritic cell, monocyte, B and NK cell deficiency. These syndromes present a wide range of

clinical features, dominated by severe infections and haematological disorders such as myelodysplastic syndrome. Up to 70% of GATA2-mutated patients have dermatological features, mainly genital or extra-genital warts, panniculitis or erythema nodosum, and lymphedema. We report 3 patients presenting with common dermatological and haematological features leading to the diagnosis of GATA2 deficiency, but also with skin manifestations that have not been previously described: gingival hypertrophy, macroglossitis and glossitis, and granulomatous lupoid facial lesions. Dermatologists can encounter GATA2-mutated patients and should recognize this disorder.

INTRODUCTION:

Heterozygous mutations of GATA2, a zinc finger transcription factor, were first described in 2011 by Hsu *et al.*¹ in patients with monocytopenia and mycobacterial infections (monoMAC). Further research has confirmed GATA2 mutations in dendritic cell, monocyte, B- and natural killer (NK-) cell deficiency², in familial myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)³ and in Emberger syndrome (primary lymphedema with myelodysplasia). Spinner *et al.*⁴ reviewed the medical records of 57 patients with GATA2 mutations and identified a broad spectrum of clinical characteristics with predominantly hematological, infectious, pulmonary, dermatological, neoplastic, vascular and lymphatic features.

We report on three GATA2-mutated patients where cutaneous features preceded the manifestations related to other organ systems.

CASE REPORTS:

Case 1:

A twelve-year-old white patient was referred to our department for lymphedema of the right lower leg, evolving since the age of eleven.

He had no medical history until he was 9 when he started to have recurrent aphta and epistaxis. At 11, he developed lymphedema of the right leg.

Physical examination evidenced bilateral lymphedema, plantar warts and gingival hypertrophy which was often hemorrhagic (Figures 1 A and B). The patient was hospitalized for cellulitis of the right leg, treated with antibiotics.

Blood cell counts revealed a normal haemoglobin level alongside macrocytosis, normal platelet count, but low levels of neutrophils, lymphocytes and monocytes. A bone marrow biopsy showed dysmyelopoiesis, without myelodysplastic syndrome, and medium megakaryocyte density without excess blasts. The bone marrow karyotype was normal. The association of congenital lymphedema, multiple warts and leucopenia pointed to Emberger syndrome. Genetic testing confirmed GATA2 mutation (c.1084C>T (p.R362X) on exon 5). Further tests are underway to investigate any deafness and to study familial GATA2 mutation status.

Case 2

A 28-year-old woman was admitted to the Respiratory department with increasing shortness of breath, dry cough and interstitial lung disease. Surgical pulmonary biopsy showed pulmonary alveolar proteinosis, and broncho-alveolar lavage evidenced lymphocytic alveolitis.

She had a history of idiopathic lymphedema affecting both lower legs, diagnosed five years earlier (Figure 1C). Lymphoscintigraphy suggested lymphatic vessel hypoplasia.

Physical examination also revealed multiple warts on the hands, sclerodermiform lesions on the legs and panniculitis on the upper limbs (Figure 1C).

Biopsies of the upper limb lesions concluded to erythema nodosum. The two biopsies showed roughly similar lesions. They were both performed in the subcutis, totally sparing the overlying epidermis and dermis. They showed thick sclerosis with horizontal, thickened and hyalinized collagen bundles associated with fragmented elastic fibers (Orcein). In the periphery some inflammatory cells were observed, grouped in clusters (Figure 1 D and E).

Long-term cultures for mycobacteria were negative in the skin biopsies.

She had an enlarged tongue with several depapillated areas, and she complained of dysgueusia (Figure 1 F).

Blood cell counts showed pancytopenia. Bone marrow biopsy was normo-cellular with three-lineage dysplasia. Myelodysplastic syndrome (MDS) without karyotype anomaly was diagnosed. She was thought to have MonoMAC syndrome, and GATA2 mutation (c.1020_1029dup (p.R3444GfsX43) on exon 5) was identified. Over 9 months, MDS remained stable but her respiratory parameters deteriorated. Hematopoietic stem-cell transplantation (HSCT) is being considered.

Case 3

A 20-year-old white woman was referred to the hematology department for pancytopenia lasting 5 years. In childhood she experienced recurrent ear, nose and throat (ENT) infections (otitis, rhinitis) and labial herpes.

She presented with fatigue, weight loss, multiple warts on both hands, and lupoid lesions of the cheeks, forehead and temples (Figure 2 A and B). These facial lesions first appeared at age fifteen and none of the different treatments (topics, metronidazole, cyclins and zinc) was effective.

Two skin biopsies were performed at 2 different times, showing a granulomatous infiltrate in the upper and mid dermis in the two lesions, located mainly between hair follicles. This infiltrate was mostly made up of histiocytes, some of them epithelioid, associated with giant multinucleated cells and neutrophils in the deeper part. (Figure 2 C).

Bacterial, mycobacterial and fungal staining tests were negative. Cutaneous cultures were negative for bacteria, mycobacteria and fungi.

Blood cell counts revealed pancytopenia (including low hemoglobin, low platelet, white blood cell, neutrophil, lymphocyte and monocyte counts). Bone marrow examination showed three-lineage dysplasia leading to the diagnosis MDS. Her karyotype was normal. A GATA2 mutation (c.1060A>C (p.T354P) on exon 5) was identified and she was diagnosed with MonoMAC syndrome.

Her parents and sister were tested, but no GATA2 mutation was detected, suggesting that the patient's disorder was caused by *de-novo* mutation.

Because of the risk of acute myeloid leukemia (AML), she underwent curative phenotypically identical allogeneic stem-cell transplantation after chemotherapy.

Five months after transplantation she had no further ENT infection and the facial cutaneous lesions rapidly healed. Blood cell counts were within the normal range and the bone marrow showed total remission. Lymphedema of both lower limbs occurred a few month after hematopoietic stem cell transplantation.

Table 1 summarizes clinical and blood test results for the 3 patients.

DISCUSSION:

GATA2 is a zinc finger transcription factor that regulates early haematopoietic differentiation, and lymphatic and vascular development. Nearly 100 GATA2 mutations have been described. They appear to cause loss of function of the mutated allele^{1,4,5}. Germline mutations arise spontaneously (*de novo*) but are then transmitted via autosomal dominant inheritance.

GATA2 mutations have been identified in more than 300 patients and 3 large cohorts of GATA2-mutated patients have been reported⁴⁻⁶.

Median age at the first clinical manifestations is 20 years (range 5 months to 78 years), although some individuals seem to have no clinical manifestation. Survival has been estimated at 91% 5 years after onset of symptoms and 67% 20 years after onset⁴⁻⁶.

GATA2-mutated patients have very heterogeneous presentations (Figure 3) and a wide range of severity, from asymptomatic to life-threatening infections, respiratory failure and leukemia.

Dermatological features appear to be secondary to several conditions. Up to 70% of patients have persistent HPV infections⁶. Severe HPV infections are recalcitrant, possibly generalized, warts and condylomata⁴⁻⁶. Absence of cellular immunity caused by the paucity of NK-cells or their dysfunction leads to these severe manifestations. Our 3 patients had numerous warts on the limbs. Patient 2 had no recurrence of warts after HSCT. Patients 1 and 3 had limited manifestations, but were resistant to the treatments instated. Patients infected with oncogenic⁷ and non-oncogenic⁸ HPVs have been reported. The majority of these

patients develop warts years before GATA2 diagnosis. They may develop HPV-related skin malignancies, including squamous intra-epithelial lesions, bowenoid papulosis and invasive squamous cell carcinoma. Early HPV vaccination is recommended after GATA2 mutation diagnosis.

Other severe infections induced by immunodeficiency in GATA2 syndromes may also entail cutaneous manifestations. Non-tuberculous mycobacterial infections have been described with dermatological manifestations such as ulcers of the lower limbs⁹ and nodular skin lesions⁴. The most frequent complication is cellulitis. Lymphedema, with early care, can be managed with compression stockings, as for patient 1 in our report. For patients 1 and 2 lymphedema was the first symptom of their disease.

Up to one third of GATA2-mutated patients have erythema nodosum or panniculitis, usually on the lower extremities. These conditions can have several causes: NTM infections, bacterial infections or auto-immune phenomena¹⁰ (lupus-like syndromes, primary biliary cirrhosis-like liver damage and multiple sclerosis-like syndrome). Here, one of the patients (Case 2) presented with sclerodermiform changes located deep in the subcutis, resembling deep morphea. Skin biopsies show panniculitis, erythema nodosum or granulomatous lesions. Bacteriological samples of nodular lesions may evidence non-tuberculous mycobacteria such as *M szulgai*, *M avium complex*, *M abscessus*.

Finally, dermatological manifestations can be neoplastic. Chronic, recurrent warts and condylomata may evolve into squamous intra-epithelial dysplasia or squamous cell carcinoma. Monitoring of patients by dermatologists is therefore important. Non HPV-related squamous-cell and basal-cell carcinomas have also been described^{10,11}. Additionally melanoma and 3 cases of Sweet syndrome are reported in the setting of underlying MDS/AML⁴.

Our patients had unusual cutaneous manifestations not described previously. Patient 1 had a history of gingival hypertrophy and recurrent aphthae. Patient 3 had a distinctive presentation involving lupoid lesions located exclusively on her face. The skin biopsy revealed granulomatous lesions with mixed acute and chronically inflammatory cells. Granulomatous skin lesions can occur in patients with immunodeficiency from diverse causes¹². In our patient, the negative microbiological investigations and the resolution after HSCT are suggestive of this mechanism. Manifestations associated with GATA-2 dysfunction are numerous, they are expressed in a large array of organs, and can be related to several causes (neoplastic, infectious, immunodeficiency). In our patients, it is difficult to ascertain the novelty of the manifestations. If gingival hypertrophy is rather non-specific, the particular presentation of facial non-infectious granulomatous dermatosis (case 3) is worth mentioning, since it has not been reported as a manifestation in other immunodeficiencies. The sclerodermiform changes (case 2) constitute a new finding, although we are unable to provide any clue to the related mechanisms.

In conclusion, we highlight both well-known and new dermatological features in the recently-described GATA2 mutation clinical spectrum. As they can precede other clinical symptoms, dermatologists are crucial in early diagnosis of this multiform disease. Dermatological monitoring is important for patients identified in order to detect or prevent HPV-related or non-HPV-related skin cancers.

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Patient Present age	Gender	Dermatologic clinical features (age at onset: years)	Haematologic signs	Age at first haematological sign	Other clinical features (age at onset: years)	Age at first visit	Age at diagnosis	GATA2 mutation Protein	Treatment (age: years)
Case 1 <u>12 years</u>	M	Recurrent aphta (9) Warts Lymphedema of lower right leg (11) Cellulitis of right lower leg (12) Gingival hypertrophy (9)	Macrocytosis Neutropenia Monocytopenia Low level of gammaglobulin (IgG) Myelodyspoiesis without MDS Normal karyotype	11 years	Epistaxis (9)	11 years	12 years	c.1084C>T p.R362X exon 5	None
Case 2 31 years	F	Bilateral lymphedema (right>left) (23) Deep morphea-like lesions (28) Glossitis (28) Telogen effluvium (29) Warts	Anemia Thrombopenia Monocytopenia MDS Hypergammaglobulinemia Normal karyotype	28 years	Pulmonary alveolar proteinosis (28) Fatigue, loss of weight (28) Phyllodes tumor of left breast (30) menometrorrhagia (29) Pulmonary pneumocystis and aspergillosis colonisation (30)	23 years	28 years	c.1020_1029dup p.R3444GfsX43 exon 5	Allogenic HSCT and pulmonary graft under consideration
Case 3 20 years	F	Recurrent labial herpes (childhood) Warts Lupoid lesions of the face (10): granulomatous aseptic lesions Bilateral lymphedema of lower legs	Anemia Thrombopenia Monocytopenia B-cell lymphopenia MDS Low level of IgA Normal karyotype	11 years	Fatigue, loss of weight (11) Recurrent ENT infections (childhood) Influenza	11 years	19 years	c.1060A>C p.T354P exon 5	Allogenic HSCT (19)



