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The Case | Proteinuria and low platelet count

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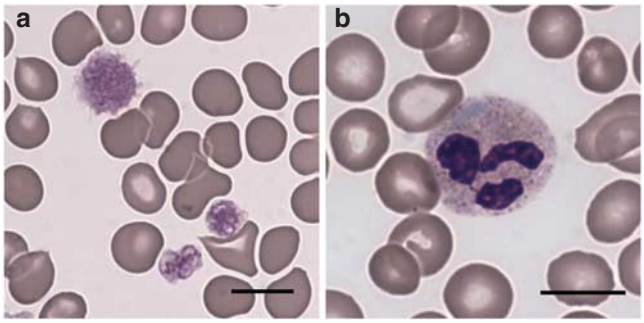

Figure 1 | Representative fields from the peripheral blood smear of our patient (a and b). May-Grünwald-Giemsa staining. Bars = 10 nm.

A 45-year-old man with moderate renal impairment (serum creatinine 1.5–2 mg/dl, CrCl 45–55 ml/min), proteinuria (0.8–1.2 g/24 h), and severe thrombocytopenia (platelet count 10–30,000/mm^3) was referred for outpatient nephrological consultation. The patient was in good general condition, working full time as a driver, with two sons in good health. His medical history was notable for hypertension, which was controlled by angiotensin-converting-enzyme inhibitors. Kidney function impairment had been known since 2001. Despite thrombocytopenia (since infancy), the patient had never suffered from spontaneous bleeding.

The physical examination was unremarkable. Initial diagnostic testing revealed no sign of autoimmune disease (negative or normal: anti-nuclear antibody, anti-ENA antibody, anti–double-stranded DNA antibody, serum immunoglobulins, complements, and C-reactive protein). Urine microscopy was unremarkable. Mild metabolic acidosis (serum HCO_3 was 20 mEq/l) and mild increase of intact parathyroid hormone (103 pg/ml) were present. Chest X-ray, electrocardiogram, and echocardiogram were normal, and renal ultrasound revealed mildly hyperechogenic, normal-sized kidneys.

The patient was born from non-consanguineous parents, both from a small southern Italian village; his father was started on dialysis at 50 years of age; he is reported to have had low platelet counts. Thrombocytopenia was reported on his mother's side as well (first-degree cousins, on regular hematological follow-up in another town). The patient's brother suffered from moderate renal impairment and thrombocytopenia.

The blood smear is shown in Figure 1.

What is your diagnosis?

SEE NEXT PAGE FOR ANSWERS

The Diagnosis | MYH9-related disease

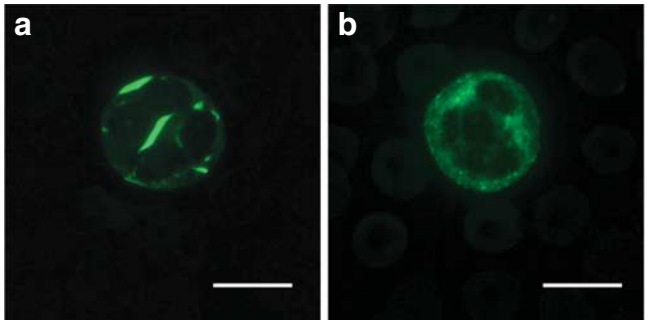

Figure 2 | Immunofluorescence localization of non-muscle myosin IIA (NMMHC-IIA) in blood smear granulocytes of the reported patient. (**a**) The MYH9 protein is typically clustered in evident cytoplasmic aggregates. (**b**) For comparison, a granulocyte from a healthy subject shows normal, diffuse cytoplasmic distribution of NMMHC-IIA. Bars = 10 nm.

The patient is affected by MYH9-related disease (MYH9-RD), an autosomal dominant macrothrombocytopenia variably associated with nephropathy, sensorineural deafness, and presenile cataract.[1–2] MYH9-RD encompasses four different presentations previously known as May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome, and Epstein syndrome.[1–3]

MYH9 encodes for the heavy chain of the non-muscle myosin IIA (NMMHC-IIA), a cytoplasmic myosin expressed in most cells and tissues. In the kidney, NMMHC-IIA is present in podocytes, mesangial, tubular, and endothelial cells.[1–2]

MYH9-RD patients have thrombocytopenia and giant platelets and develop one or more extra-hematological manifestations during childhood or adulthood.

The peripheral blood smear shows thrombocytopenia and marked platelet macrocytosis, with some platelets being equal in size to or even larger than erythrocytes ('giant platelets'; Figure 1).

Granulocytes present 'Döhle-like' bodies: basophilic, light-blue cytoplasmic inclusions, round or spindle shaped, with major diameter of 2–7 μm. 'Döhle-like' inclusions in granulocytes are pathognomonic, although they are not evident in 18–56% of affected subjects.[1–2] Ophthalmologic evaluation (normal in our patient) and audiometric testing (which showed sensorineural hearing loss for high frequencies >2000 Hz) may further refine the clinical hypothesis.

Kidney involvement is characterized by proteinuria, microhematuria, and progression to renal failure.[1–3] Renal pathology has rarely been described, partly because thrombocytopenia limits the feasibility of renal biopsy. The most frequently reported picture is focal segmental glomerulosclerosis.[1–3]

In our patient, the family tree highlighted the association of proteinuria, renal function impairment, and thrombocytopenia in the patient's brother, two male cousins, and one nephew. The finding of chronic kidney disease and low platelets counts on both mother's and father's side could be misleading, as inheritance of MYH9-RD is autosomal dominant.

However, both parents came from an isolated, southern Italian village, and an effect of a common ancestor can be hypothesized. Indeed, clusters of autosomal dominant diseases are not rare in such a setting.

The diagnostic suspicion is confirmed by immunofluorescence of the blood smears (Figure 2). The NMMHC-IIA granulocyte aggregates are specific to MYH9-RD and are recognizable in all patients with MYH9 mutations.[1] Mutational screening confirms the diagnosis and provides a prognostic assessment. Our patient displayed the c.4270G>C mutation in exon 30 (substitution of aspartic acid at residue 1424 of the C-terminal domain of NMMHC-IIA with histidine). According to the currently defined genotype–phenotype relationships, he belongs to a subset of cases with slow chronic kidney disease progression, who benefit from support therapy including angiotensin-converting-enzyme inhibitors and/or angiotensin receptor blockers, low protein diet, strict control of blood pressure, and calcium–phosphate and acid–base balance.[2–3]

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