CASE REPORT

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Indication of total parathyroidectomy for an Epstein syndrome patient with end-stage renal disease

DANIELA MARINESCU[1)], ELENA-CĂTĂLINA BICĂ[2)], MIRELA-CORINA GHILUŞI[3)], MARIUS BICĂ[1)], ANA-MARIA PĂTRAŞCU[4)], ŞTEFAN PĂTRAŞCU[1)], STELIAN PANTEA[5)], VICTOR DAN EUGEN STRÂMBU[6)], VALERIU ŞURLIN[1)], NICOLAE-DRAGOŞ MĂRGĂRITESCU[1)], KONSTANTINOS SAPALIDIS[7)], IONELA ROTARU[4)]

[1)]*Department of Surgery, University of Medicine and Pharmacy of Craiova, Romania*

[2)]*Department of Pediatrics, University of Medicine and Pharmacy of Craiova, Romania*

[3)]*Department of Pathology, University of Medicine and Pharmacy of Craiova, Romania*

[4)]*Department of Hematology, University of Medicine and Pharmacy of Craiova, Romania*

[5)]*Department of General Surgery, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

[6)]*Department of Surgery, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

[7)]*Department of Surgery, Aristotle University of Thessaloniki, Thessaloniki, Greece*

Abstract

Epstein syndrome is an extremely rare genetic disorder characterized by the association of nephritis, deafness and megathrombocytopenia. We present the case of a 21-year-old patient diagnosed with Epstein syndrome and hyperparathyroidism secondary to chronic kidney disease. The main particularity of this case resides in the association between megathrombocytopenia and secondary hyperparathyroidism requiring surgery, which could lead to a series of concerns regarding the intra- and postoperative hemorrhagic risk of the procedure. Nevertheless, both the surgical procedure and the postoperative recovery were uneventful, suggesting that the lower threshold for preoperative thrombocyte count in megathrombocytopenia should be specifically considered on an individual case analysis.

Keywords: Epstein syndrome, thrombocytopenia, hyperparathyroidism, end-stage renal disease.

Introduction

Epstein syndrome (ES) is a rare genetic disease caused by a heterozygous mutation in the non-muscle myosin heavy chain 9 (*MYH9*) gene on chromosome 22, first described by Epstein in 1972 [1]. This autosomal disorder is characterized by nephritis, deafness and thrombocytopenia with macrothrombocytopathia. Although some of the symptoms, such as nephritis and deafness, are similar to those found in Alport syndrome, most of the common features described in ES are also shared with several other disorders caused by the mutation in *MYH9* gene, such as Sebastian and Fechtner syndromes, as well as May–Hegglin anomaly [2–4]. Therefore, some authors suggested that all these genetic diseases should be considered as variable expressions of a single disorder, termed as "*MYH9*-related disease". However, the absence of Döhle body-like leukocyte inclusions in peripheral blood smear tends to differentiate ES from other *MYH9*-related conditions.

One of the main concerns regarding ES is its constant association with chronic kidney disease, whose progressive evolution to end-stage renal disease (ESRD) invariably leads to multiorgan chronic damage and prompts the necessity for hemodialysis or peritoneal dialysis. Phosphocalcium metabolism alteration due to ESRD-induced hyperparathyroidism causes bone changes, secondary demineralization, strength and bone volume disorders. In the skeletal remodeling process, an imbalance between resorption and bone formation usually occurs, resulting in osteodystrophy, osteomalacia and fibrous osteitis with debilitating symptoms and signs. All these pathological alterations can be controlled either pharmacologically or, in unresponsive cases, by surgery.

Case presentation

We present the case of a 21-year-old male patient with Epstein syndrome, rapidly progressive glomerular nephropathy, ESRD requiring hemodialysis and severe bone disease due to secondary hyperparathyroidism. The patient was admitted in the Department of General Surgery, Emergency County Hospital of Craiova, Romania, with the diagnosis of ESRD, secondary hyperparathyroidism, bilateral hearing loss, macrothrombocytopenia and Epstein syndrome.

The disease apparent onset was in the context of a previous surgical intervention (appendectomy) performed nine years ago, when thrombopathy, average bilateral hearing loss, chronic renal disease and hypertension were noted, pleading for the diagnosis of Epstein syndrome. Additional tests were considered: biological samples indicated severe microcytic anemia and high urea and creatinine levels, while urine analysis showed hyaline cylinders. Other investigations included chest X-ray, heart and abdominal ultrasound, indicating no pathological alterations except for hyperechoic renal cortex. Audiometry

showed average bilateral sensorineural hearing loss. Renal biopsy confirmed pathological glomerular lesions. Treatment was initiated with Prednisone and Cyclophosphamide. Notwithstanding the evolution of the disease was unfavorable, as cardiomegaly was certified by subsequent chest X-ray and heart ultrasound, as well as suprahepatic veins hyper-pressure syndrome with venous dilatation and ascites on abdominal ultrasound. Renal function rapidly depreciated and a chronic hemodialysis program was initiated. However, despite altered morphological and quantitative thrombocyte pattern, during the nine years of hemodialysis the patient displayed no hemostasis disorders at the end of hemodialysis sessions and did not required special measures for hemostasis.

ESRD was complicated by renal bone disease manifested by major osteoarticular pain during both active and passive mobilization of the limbs. Subsequently, the patient was diagnosed with secondary hyperparathyroidism and began medical therapy to correct the secondary endocrine dysfunction. Unfavorable clinical evolution after adequate pharmacological treatment, as well as parathyroid hormone (PTH) values of over 2000 pg/mL pleaded for elective total parathyroidectomy.

On this current admission, the patient presented with osteoarticular pain, pelvic mobilization deficiency, and a patent arteriovenous fistula with arterialized vein without aneurysm. Biological values were normal, except for mild anemia with anisocytosis and hypochromia, high creatinine values, PTH level 2200 pg/mL and thrombocytopenia (16 000/mm^3).

The patient displayed no clotting disorders, but severe thrombocytopenia was an absolute contraindication for elective surgery.

The hematological consultation indicated short-term Dexamethasone therapy and capillary blood smear with platelet quantity and quality assessment at the end of treatment. Hematological smear examination revealed megathrombocytes and reduced number of platelets counted on the field due to incomplete proplatelet fragmentation (Figures 1 and 2).

Surgery was indicated when a safe value of no less than 100 000 platelets/mm^3 was observed and total parathyroidectomy was performed. Four parathyroid glands with dimensions ranging between 2×1 cm and 0.5×1 cm were excised and substitution treatment with Calcium i.v. was instated (Figures 3 and 4). Postoperative recovery was uneventful and the patient was discharged with a Ca^{2+} value of 8.6 mg/dL.

Measurement of immediate postoperative PTH revealed values less than 100 pg/mL with significantly improved osteoarticular symptoms after six weeks.

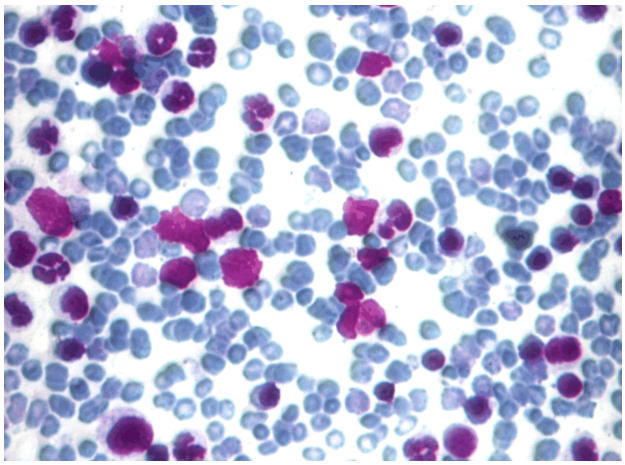

Figure 1 – ***Peripheral blood smear: megathrombocytes with reduced number of platelets counted on the field [May–Grünwald–Giemsa (MGG) staining, ×40].***

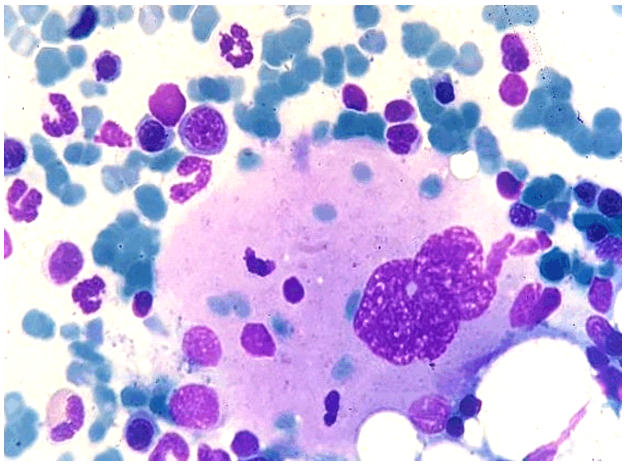

Figure 2 – ***Blood marrow smear: megakaryocyte and megathrombocytes (MGG staining, ×100).***

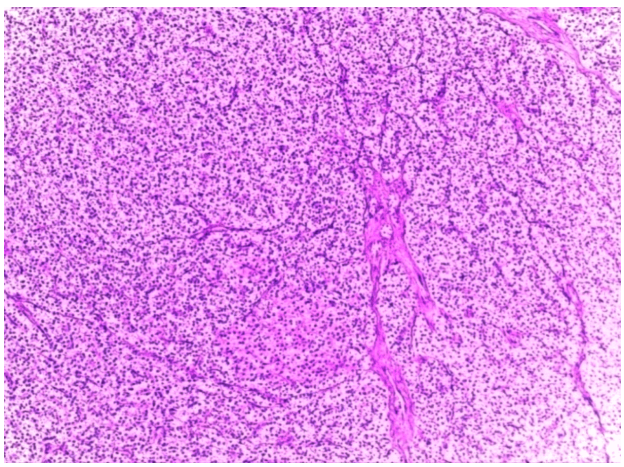

Figure 3 – ***Parathyroid gland: chief cells and oxyphilic cells hyperplasia [Hematoxylin–Eosin (HE) staining, ×100].***

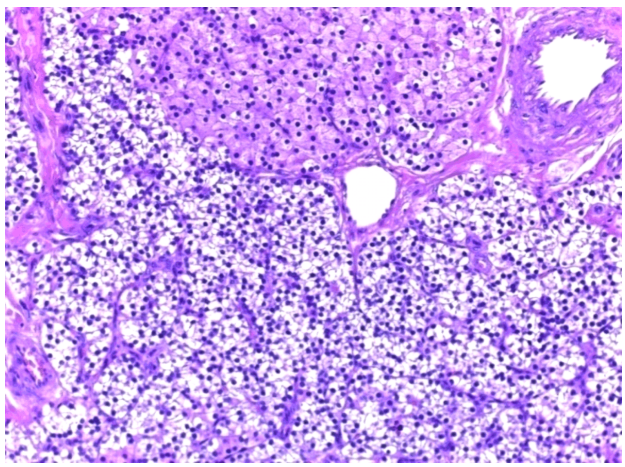

Figure 4 – ***Parathyroid gland: water clear cells and chief cells hyperplasia (HE staining, ×200).***

Discussions

Epstein syndrome is an autosomal dominant disorder caused by a mutation in the *MYH9* gene on chromosome 22q12, which associates thrombocytopenia with megathrombocytopathia, glomerular kidney damage and mild hearing loss. For this specific case, the diagnosis of ES was difficult to establish as ES shares many similarities with other *MYH9*-related diseases and with Alport syndrome. However, the presence of specific leukocyte inclusions in case of Sebastian syndrome or May–Hegglin anomaly, as well as the early onset of hematuria, the low life expectancy for male patients and, most importantly, the uncommon occurrence of megathrombocytopenia in case of Alport syndrome can provide important diagnostic clues for ES [5].

The main particularity of this case resides in the association between ES and secondary hyperparathyroidism due to ESRD. Although the indication for parathyroidectomy was undeniable, the association of thrombocytepenia and megathrombocytemia in ES could raise a series of questions about the potential hemorrhagic risk of the procedure. However, as no severe bleeding occurred neither during surgery nor in the postoperative course, it appears that these concerns tend to be overstated. Moreover, for perioperative blood management, it seems reasonably to suppose that the minimal safe limit for thrombocytopenia with normal platelet morphology is different than that of ES, which is characterized by severely altered thrombocytes.

Nowadays, it is known that half of the hereditary thrombocytopenia cases are caused by a *MYH9* gene mutation [6–9]. Thrombocytopenia is responsible for spontaneous bleeding when it is less than 20 000/mm^3. Likewise, there are reported ultrastructural and adhesion defects in the structure of thrombocytes which directly affect bleeding times [10–15]. Macro- or megathrombocytopenia, commonly found in most of the *MYH9* syndromes, are defined as morphological abnormalities where a low number of thrombocytes is associated with a high thrombocyte volume [16, 17]. Taking this aspect into consideration, special care had been paid for this case to differentiate megathrombocytopenia from pseudothrombocytopenia, which is usually considered nothing but a laboratory artifact, characterized by large size platelet aggregates that makes them appear in smaller numbers on the field count [17–20]. There are, however, two diagnostic limitations of this study: the absence of molecular genetic studies – especially the *MYH9* gene – and the lack of inheritance pattern assessment.

Another aspect complicating the paradigm of this case is the addition of end-stage renal disease. ESRD is a common finding in most of these syndromes and usually induces a metabolic response defined by endocrine and electrolyte imbalances of the phospho-calcium metabolism and vitamin D, due to secondary parathyroid hyperplasia. These metabolic and endocrine dysfunctions, defined by increases in serum levels of PTH, increases of serum calcium and serum phosphorus levels, as well as a decrease in 1,25$(OH)_2$-vitamin D3 and bone demineralization, lead to pathological changes in the bones and soft tissues.

The most serious complications usually refer to pathological fractures, valvular disease, mediocalcinosis with peripheral arterial disease and chronic cerebrovascular risk of fatal and non-fatal stroke [5]. Mediocalcinosis, consisting in a calcar impregnation of the arterial media, progressively leads to a systemic and peripheral vasculopathy, which increases the risk of cardiovascular events, but also depletes the vascular bed for optimal vascular access site in hemodialysis program, thus requiring conversion to peritoneal dialysis. All these consequences are the result of reduced kidney function in ESRD with a significant decline in vitamin D production, decreased tubular reabsorption of calcium and increased phosphorus absorption. Furthermore, ESRD dialysis can only replace part of renal function – that of purging – but not the other complex functions of the kidney.

The consequence of these changes is an adaptive response of the parathyroid glands. Hyperparathyroidism is associated with the hypertrophy and hyperplasia of the parathyroid glands and late nodular transformation. Consequently, PTH levels gradually increase from normal levels of 60 to 70 pg/mL to values more then 200 pg/mL.

When survival in dialysis program is longer, as in this case, the implications of secondary hyperparathyroidism tends to be of greater severity thus requiring parathyroidectomy [1]. Our patient had a clear indication for parathyroidectomy, but thrombocytopenia made a clear contraindication for surgery. According to the current guidelines for elective surgery, there was a clear contraindication for surgical procedure due to severe thrombocytopenia [21]. However, we consider that any such event should be carefully evaluated given the clinical and biological particularities of this genetic anomaly and its exceptional occurrence.

Conclusions

In the rare instance when ESRD patients on hemodialysis is subjected to total parathyroidectomy due to secondary parathyroidism, thrombocytopenia less than 100 000/mm^3 is considered *ab initio* an absolute contraindication for elective surgery. Instead, every report of macrothrombocytopathia and thrombocytopenia associated to severe glomerular disease should be thoroughly investigated on a case-by-case basis, so that further diagnostic tests and adequate therapy to be carried out.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Elena-Cătălina Bică and Stelian Pantea had equal contribution to the first author thus share main authorship for this study.

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Corresponding authors

Ştefan Pătraşcu, Assistant Professor, MD, PhD, Department of Surgery, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Dolj County, Romania; Phone +40724–216 642, e-mail: stef.patrascu@gmail.com

Nicolae-Dragoş Mărgăritescu, Lecturer, MD, PhD, Department of Surgery, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Dolj County, Romania; Phone +40723–271 941, e-mail: dmargaritescu@yahoo.com

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