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Letter to the Editor

Clinical course and management of adult-onset immune-mediated cytopenia associated with Kabuki syndrome

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To the Editor,

Kabuki syndrome (KS) is a rare genetic disease characterized by congenital malformations, growth deficiency, mental retardation and altered immune regulation [1]. Autoimmune cytopenias may develop throughout childhood, with immune-mediated thrombocytopenia (ITP) being the most prevalent one. Sporadic cases of immune-mediated haemolytic anaemia and neutropenia have also been reported [1,2]. The clinical course of two patients diagnosed with KS in infancy who developed cytopenia as young adults is described. Both responded to the standard treatment of immune-mediated cytopenia developing in the adult non-KS population.

Case 1 was a 29 year-old male patient who presented to the hospital on October 23rd 2013 for persistent oral mucosal bleeding. On admission his platelet count (Plt) was 1×10^9/L, white blood cell (WBC) count 10.9×10^9/L and haemoglobin 15.7 g/dL. A peripheral blood smear confirmed severe thrombocytopenia with no associated abnormalities of leukocytes or erythrocytes. Blood counts performed on a regular basis in the preceding years, showed slow, progressive decline in platelet counts which were normal (Plt 247×10^9/L) in 2006 and constantly around or below 150×10^9/L after year 2011; last platelet count available, in May 2013, was 154×10^9/L. The patient was hospitalized and received initial treatment with dexamethasone 40 mg/day for 4 consecutive days with no rise in platelet counts. He was therefore switched to oral prednisone 1 mg/kg/day; two courses of intravenous immunoglobulins were also administered. Platelet counts rose starting from day +23 from therapy start; at discharge from the hospital, on day +34, his platelet count was 159×10^9/L. A thorough work-up for ITP was performed. Anti-platelet antibodies, direct test, was positive for GP IIb/IIIa; auto-antibodies (anti-thyroid, anti-DNA, anti-nuclear antibodies, extractable nuclear antigens antibodies) were all negative; gammaglobulin and IgA levels were normal. Serology for HCV, HBV and HIV was negative; Helicobacter pylorii faecal antigen was negative. Abdomen sonography revealed normal spleen, 9 cm in diameter, and a horse shoe kidney (known to be associated with KS) with no other associated pathological findings. Bone marrow examination showed normal cellularity with megakaryocytic hyperplasia, consistent with a diagnosis of ITP. Cytogenetic analysis disclosed a normal karyotype. Prednisone was slowly tapered off over the following 3 months; platelet count at therapy discontinuation was 174×10^9/L. Except for moderate weight gain, steroid therapy was well tolerated; specifically, no infectious episodes were recorded. Response to treatment is shown in Fig. 1. On March 15th 2014 he was re-admitted to another hospital for abdominal pain; sonography revealed multiple splenic infarcts whose nature could not be disclosed after extensive work-up. In face of the risk of splenic rupture, the patient was transferred to our hospital to undergo laparotomic splenectomy; platelet count at surgery was 221×10^9/L. Surgery was complicated by severe respiratory insufficiency secondary to bilateral pulmonary infiltrates, which required non-invasive respiratory support and prolonged anti-microbial therapy; no specific microorganism was isolated. Histology on the surgical spleen specimen showed white pulp hyperplasia. Subsequent follow-up was otherwise uneventful and at last out-patient visit in April 2019 he was well with platelet count of 265×10^9/L and neutrophil count of 5.1×10^9/L.

Case 2, was a 23 year-old male patient presenting to the hospital in August 2015 for fever associated with non traumatic minor skin and oral bleeding. On admission his platelet count was 7×10^9/L, WBC count 2.33×10^9/L with an absolute neutrophils count of 0.8×10^9/L and haemoglobin 12.7 g/dL. A peripheral blood smear confirmed presence of severe thrombocytopenia and neutropenia (neutrophils 3%) and absence of immature lymphoid/myeloid cells. He underwent bone marrow examination which ruled out acute leukaemia; myeloid and megakaryocytic hyperplasia were found. No monoclonal T or B cell clones were found in bone marrow and peripheral blood. Cytogenetic analysis disclosed a normal karyotype. Anti-platelet antibodies were positive, both direct (GP IIb/IIIa, Ib/IX, Ia/IIa) and indirect (GP IIb/IIIa) test; anti-neutrophils IgG antibodies – both direct and indirect test - were also positive. Gammaglobulin level was normal. Abdomen sonography revealed a slightly enlarged (13 cm in diameter) but otherwise normal spleen and a horse shoe kidney with no other pathological findings.

A diagnosis of combined immune-mediated thrombocytopenia and neutropenia was made and the patient was started on methylprednisolone 1 mg/kg/day for 5 days and then switched to a high-dose pulsed dexamethasone regimen (20 mg/day for 2 additional days without subsequent tapering) in order to minimize the infectious risk in face of the severe neutropenia. Haematological response was obtained on day

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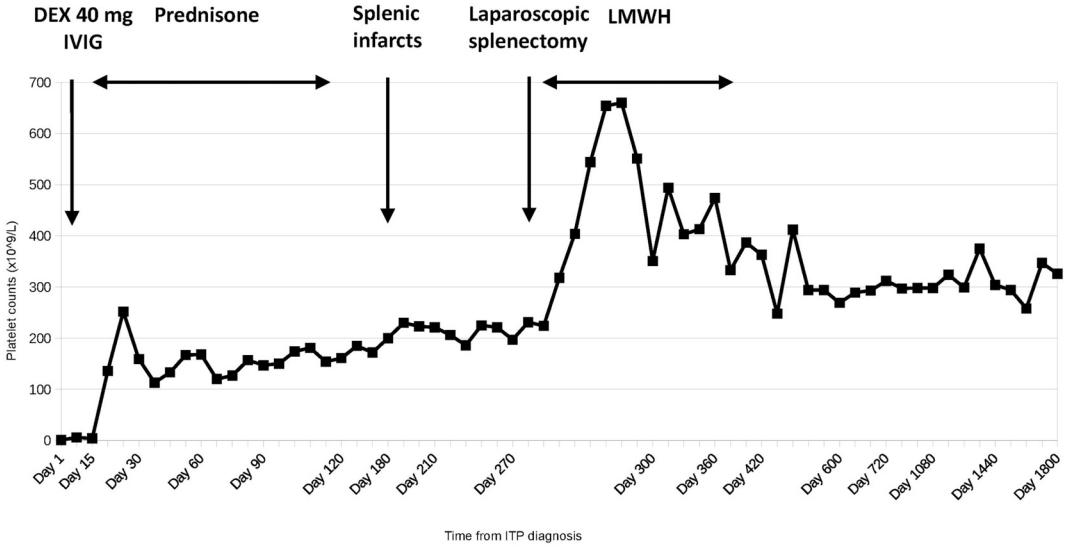

Fig. 1. Case 1: platelet count in response to treatment and at follow-up. DEX: dexamethasone; IVIG: intravenous immunoglobulins; LMWH: low molecular weight heparin.

3 of therapy with platelets rising from 7 to 54 $\times$ 10^9/L and neutrophils rising from 0 to 0.140 $\times$ 10^9/L. The patient was discharged on day 7 from admission with platelet count 182 $\times$ 10^9/L, neutrophils 1.2 $\times$ 10^9/L, haemoglobin 12.6 g/dL. After discharge he completed 6 courses of pulsed dexamethasone 20 mg/day for 4 days every 3 weeks (last course in December 2015) with full recovery of platelet and neutrophil counts. Therapy was well tolerated and no infectious episodes were recorded.

In April 2016 his platelet counts started to decline and in June 2016 isolated severe thrombocytopenia recurred. In view of the prompt response to steroids and lack of side effects, he was started on oral full-dose dexamethasone (i.e. 40 mg/day for 4 consecutive days) with prompt complete recovery of platelet counts.

In-labelled platelet survival study, performed after platelet recovery, was consistent with splenic and hepatic uptake with only slightly reduced platelet life span (6 days, normal 7–10 days). He received 3 additional courses of dexamethasone (last course administered on September 7th 2016) which were well tolerated and resulted in complete recovery of platelet counts which remained stable until January 2017. A second relapse – platelet count of 9 $\times$ 10^9/L - occurred on February 9th 2017, 6 months after completion of the second high-dose dexamethasone treatment. Dexamethasone 40 mg/day for 4 days was started and laparoscopic splenectomy was scheduled and performed on March 15th. Post-operative course was uneventful and the patient was discharged on March 18th with a platelet count of 259 $\times$ 10^9/L on prophylactic heparin. Histology on the surgical spleen specimen showed white pulp hyperplasia. At last follow up visit in June 2019 the patient was in complete response with a platelet count of 220 $\times$ 10^9/L and a neutrophil count of 4.0 $\times$ 10^9/L. Response to treatment is shown in Fig. 2.

Management of patients with orphan conditions is increasingly becoming an issue for the haematologist but also for the internal medicine professional, since the diagnostic threshold is lowering, survival is ameliorating, and mild forms may be disclosed in adulthood. Kabuki syndrome, also named Niikawa-Kuroki syndrome, is a rare multi-systemic disorder linked, in the majority of cases, to mutations of two genes - KMT2D or KDM6A - both involved in the epigenetic regulation of DNA and histone proteins [1]. The syndrome owes its name to the peculiar facial features of affected individuals which resemble the make-up of actors in Kabuki, the traditional Japanese theatre. Clinical and/or laboratory features of immune dysfunction – e.g. immune-mediated cytopenias, vitiligo, thyroiditis, hypogammaglobulinemia - have been described in approximately 20% of paediatric case series of KS patients [2]. A recent review on the immunological derangement associated with KS [3], summarizes data on 76 paediatric cases with some form of immune dysfunction presented in the literature. Of these, 22/76 (29%) were diagnosed with immune-mediated peripheral cytopenia(s). ITP seems to be the most frequent among immune-mediated cytopenias, but cases of haemolytic anaemia and/or neutropenia, either combined with ITP or presenting as single-line cytopenia, are also reported.

Contrary to paediatric ITP arising in the general population - which is most often an acute-onset, self-limiting disorder not necessarily requiring specific treatment - ITP associated with KS has been reported to run a chronic relapsing course with sub-optimal response to standard first-line therapy with corticosteroids [2,4,5]. This peculiar clinical course has been attributed to the presence of an underlying immune defect characteristic of KS [2–4]. From a pathogenic point of view, a link between KS and the emergence of “prohibited” self-reacting lymphoid clones has been hypothesized: somatic KMT2D mutations have been recently reported in 69% of patients with cold autoimmune haemolytic anaemia, being very similar to those occurring in KS. Such mutations, leading to KMT2D loss of function, provoke increased B cell proliferation, interferes with class switch recombination, and may concur to immune tolerance break [6]. Furthermore, histone modifications, associated with KMT2D and KDM6A mutations in KS, may alter T and B lymphocytes differentiation resulting in defective B cell maturation and Treg generation. [3].

To the best of our knowledge, no reports on the clinical course and response to therapy of adult-onset immune-mediated cytopenia(s) in KS patients are available.

The two cases presented suggest that response to standard ITP treatment of KS patients is similar to that of the general population. Administration of corticosteroids – either prednisone or pulsed high-dose dexamethasone – is well tolerated with no significant increase in infectious complications. In patients with concomitant ITP and severe neutropenia – as in case 2 - pulsed dexamethasone may be preferred in order to minimize the risk of infection. However, the increased susceptibility to infections of KS patients still needs to be carefully considered, as suggested by the severe pulmonary infection - not associated with hypogammaglobulinemia - which developed after splenectomy in patient 1. Moreover, in view of the unexplained thrombotic event occurring in patient 1, thrombopoietin mimetics should probably be used with caution in these patients.

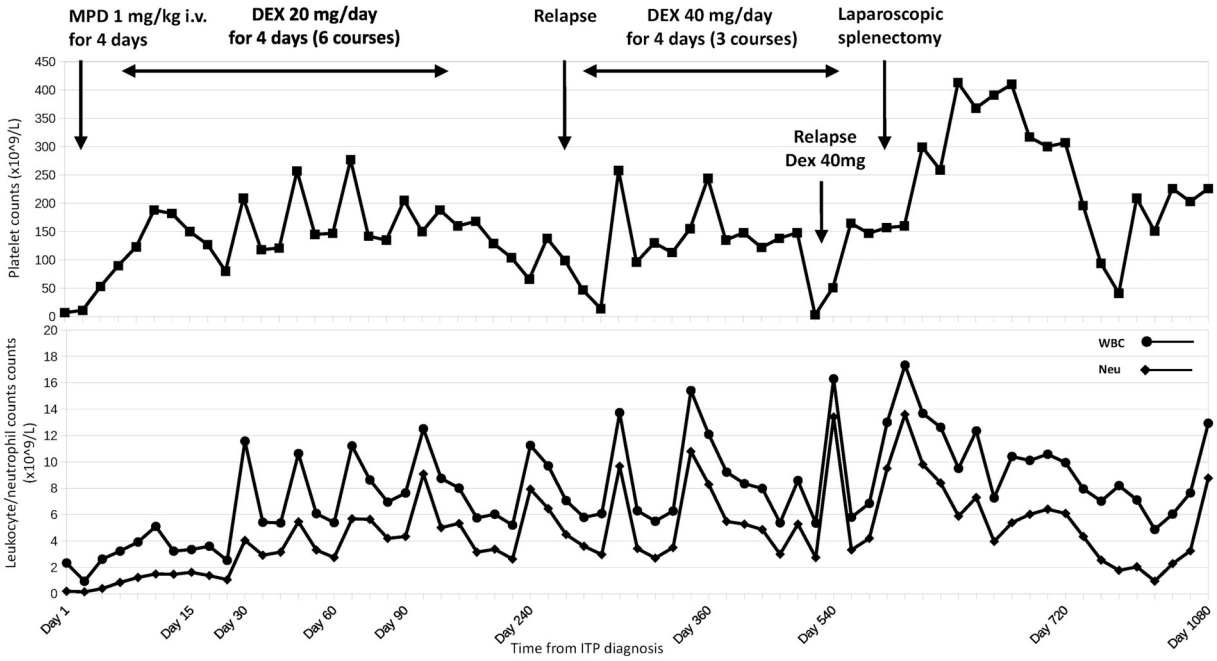

Fig. 2. Case 2: (upper panel) platelet count in response to treatment and at follow-up; (lower panel) white blood cell count (circles) and absolute neutrophil count (squares) in response to treatment and at follow-up. MPD: methylprednisolone; DEX: dexamethasone; WBC: white blood cell count; Neu: neutrophil count.

Declaration of Competing Interest

All authors declare that they have no competing interests to disclose.

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