A 12-year-old boy with X-linked agammaglobulinaemia who had breakthrough infection, thrombocytopenia and acute renal failure

AMANJIT BAL, AMIT RAWAT, RITAMBHRA NADA, SURJIT SINGH

THE CASE
A 12-year-old boy first presented to the Advanced Paediatric Centre, Post Graduate Institute of Medical Education Research, Chandigarh in October 2002 when he was 6 years old with complaints of recurrent episodes of chest infection since he was 4 years old. On examination he was 106 cm tall, had clubbing, atrophic tonsils but no palpable lymph nodes. A chest X-ray showed bilateral lower zone consolidation, a normal sweat chloride level of 31 mEq/L (normal range: 10–35 mEq/L), non-reactive HIV serology and a normal nitroblue tetrazolium dye reduction test. Bronchoalveolar lavage culture grew *Pseudomonas aeruginosa*. The serum immunoglobulin levels were markedly reduced with an IgG level of <211 mg/dl (normal range: 818–1885 mg/dl). The peripheral blood immunophenotyping by flowcytometry showed a CD3 (T cell) percentage of 74.8% (normal range: 55%–82%) and CD19 (B cell) percentage of 0.08% (normal range: 9%–29%; Fig. 1). The phytohaemagglutinin stimulation index was 2.9 (normal range: 10–15). Based on the above investigations and his clinical history a diagnosis of X-linked agammaglobulinaemia (Bruton’s agammaglobulinaemia) was made. The child was treated with a combination of ceftazidime and tobramycin. He was also started on replacement intravenous immunoglobulin (IVIG) therapy (0.4 g/day) and prophylactic co-trimoxazole.

During the second admission in January 2006, the child had fever and cough with expectoration. A CT scan at that time showed bilateral, predominantly central, bronchiectasis with collapse of the left lower lobe. He was started on cefazidime, cloxacillin and amikacin. He was admitted again in March 2006 in the paediatric surgery unit for a lobectomy for bronchiectasis which was done on 9 March 2006. Histopathological examination of the excised lobe confirmed the presence of bronchiectasis. Chest physiotherapy was advised. In June 2006 the child was admitted again with complaints of fever and cough with expectoration. The sputum culture yielded a mixed flora and the child received antimicrobials. His height now was 116 cm and haemoglobin 7 g/dl.

During the last admission on 3 October 2008 the child presented with fever for 8 days, and cough and difficulty in breathing for 2 days. Physical examination now showed a height of 130.5 cm, weight of 22.2 kg and a head circumference of 52 cm. His heart rate was 128/minute, blood pressure 98/62 mmHg and capillary filling time was <3 seconds. Clubbing was present. There was no pallor, cyanosis or jaundice. Chest examination showed bilateral symmetrical decreased expansion with an operative scar on the left side, the percussion note was dull on the left side below the third intercostal space and crepitations were present. Abdominal examination was unremarkable. No abnormality was detected on examination of the cardiovascular and central nervous systems. Haematological investigations done during the last admission showed persistent leucocytosis and thrombocytopenia. The erythrocyte sedimentation rate was 62 mm and the peripheral blood smear showed mirocytic hypochromic red blood cells (Table I).

Flowcytometric immunophenotyping showed markedly reduced proportion of CD19+ B cells (Fig. 1). The results of the other investigations are given in Tables II to IV.

The blood culture on 3 October 2008 was sterile while the tracheal aspirate on 10 October yielded *Acinetobacter* species with no growth of fungi or mycobacteria. Chest X-ray on 3 October 2008 revealed bilateral lobar consolidation and on 13 October 2008 showed evidence of acute respiratory distress syndrome.

**Course and management**
From 3 to 5 October 2008, the patient was treated for pneumonia with ceftriaxone, cloxacillin and amikacin. There was worsening of respiratory distress and the child went into shock. He was intubated, put on intermittent positive pressure respiration (IPPR) and started on inotropic support in the form of dopamine, dobutamine and adrenaline. Additional IVIG (1 g/day) was given.

**Table I. Complete blood counts in October 2008**

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**Fig. 1. Flowcytometric immunophenotyping showing markedly reduced number/proportion of CD19+ cells (B cells)**
examination showed that the child had a severe underlying illness. The child had clubbing and failure to thrive. In fact the initial clinical immediate hospital admission and a complete work-up. In addition, recurrent pneumonia especially X-ray proven pneumonia would warrant respiratory tract infections which one would tend to ignore. Recurrent pneumonia is a red-flag sign, unlike recurrent upper pneumonia since early childhood. To any paediatrician a history of terminal illness.

**DIFFERENTIAL DIAGNOSIS**

**Dr Surjit Singh:** The points for discussion in this case would be (i) the initial diagnosis of X-linked agammaglobulinaemia (XLA), (ii) the follow up from 6 to 12 years of age, and (iii) the terminal illness. The initial diagnosis of XLA was based on a history of recurrent pneumonia since early childhood. To any paediatrician a history of recurrent pneumonia is a red-flag sign, unlike recurrent upper respiratory tract infections which one would tend to ignore. Recurrent pneumonia especially X-ray proven pneumonia would warrant immediate hospital admission and a complete work-up. In addition, the child had clubbing and failure to thrive. In fact the initial clinical examination showed that the child had a severe underlying illness. Based on this we had suspected immunodeficiency after ruling out cystic fibrosis and other disorders such as Kartagener syndrome which can mimic an immunodeficiency.

In a patient with immunodeficiency, the first possibility to be considered is a secondary immune deficiency because it is much more common than primary immunodeficiency. It is easy to exclude causes of secondary immunodeficiency which are obvious on physical examination, e.g. the child may be malnourished or may be having nephrotic syndrome. However, at present, the most common cause of secondary immunodeficiency is HIV infection. This was ruled out by the non-reactive HIV serology. The remaining possibility is of primary immunodeficiency. The investigations for primary immunodeficiency can be complex, particularly if laboratory investigations are performed without taking into consideration the clinical context. However, if the process is gone through methodically there are several clinical pointers by which it is possible to narrow down the possible specific primary immunodeficiency and perform only one or two relevant laboratory investigations. In this child, we had some clues for a primary immunodeficiency on physical examination in the form of atrophic tonsils and non-palpable lymph nodes. These two physical findings are important in the context of a child with a history of recurrent infections and suggest one of two clinical possibilities—severe combined immunodeficiency (SCID) and XLA. In all other causes of primary immunodeficiency the lymph nodes would not only be palpable, but would be larger than normal. SCID presents in the first few months of life. The infections are usually polymicrobial (bacterial as well as fungal and viral), severe and life-threatening requiring repeated hospitalization. This child had never been admitted to hospital till he presented to us at 6 years of age. Most children with SCID succumb in the first year of life unless they are diagnosed early and treated with bone marrow transplantation. Since our patient had none of these clinical findings, and had survived without any prior hospitalization till the age of 6 years, SCID was unlikely. A normal CD3 (T cell) count by flowcytometry ruled it out. After ruling out SCID, XLA remains the only possibility on clinical grounds. Children with XLA unlike SCID usually present in the later half of infancy after 6 months of age. The commonest presentation in these children is recurrent pneumonia, as in this child. These infections are usually bacterial and respond to broad spectrum antimicrobials. This child had been treated with antimicrobials for recurrent pneumonia on several occasions and had responded each time. In children with XLA, prolonged survival is possible even without IVIG support provided the infections are adequately treated with antimicrobials. Laboratory finding of agammaglobulinaemia confirmed the diagnosis. However, agammaglobulinaemia can occur in several other primary immunodeficiencies other than XLA. Hence, to confirm the diagnosis of XLA, we did a CD19 assay. In the presence of agammaglobulinaemia along with absent B cells by CD19 assay, XLA is the only possible diagnosis. B cell number would be normal in other humoral immunodeficiencies such as common variable immunodeficiency (CVID) and transient hypogammaglobulinaemia of infancy (THGI). In XLA the defect is in maturation from pre-B to B-cell ontogeny unlike CVID and XLA, where the defect is in maturation from mature B cells to plasma cells.

The second issue in this case was the occurrence of frequent breakthrough infections on follow up from 6 to 12 years of age. Following a diagnosis of XLA, children are usually treated using replacement therapy with IVIG. This therapy is expensive and many of our patients cannot afford it. In resource-rich countries, most
immunologists would treat these children with 800–1000 mg/kg IVIG every month. Such dosages are too expensive for our patients and hence we routinely use a lower dose (400 mg/kg) given every 3–4 weeks, as was done in this child too. We had difficulty in maintaining the trough levels of IgG at >400 mg/dl which is usually required in most patients with humoral immunodeficiency.

Hence, it was not surprising that the child had frequent breakthrough infections though these responded to antimicrobials. It is also not a surprise that the child developed bronchiectasis. Even with better IVIG preparations and IgG trough levels >400 mg/dl, up to 15% of such patients develop bronchiectasis. The short stature in this child was probably because of chronic ill-health. However, there is a form of XLA which is associated with growth hormone (GH) deficiency.

The Bruton tyrosine kinase (Btk) gene is a large gene with 19 exons and located close to the gene for GH on the X chromosome. Hence, a variant of XLA with GH deficiency occurs due to linkage of Btk with the GH gene. However, the child had gained 7 cm over the past 1 year, ruling out an inherited GH deficiency linked to XLA.

The course of disease in our patient from 6 to 12 years of age was consistent with our expectations, especially when the diagnosis had been made after infancy by which time the lungs have undergone some permanent damage.

The third issue to be discussed in this child was the terminal illness. He had severe necrotizing pneumonia, probably caused by infection with encapsulated bacteria, which children with XLA are predisposed to. The anaemia could be multifactorial but was most probably nutritional in origin. Autoimmune haemolysis has also been implicated in children with XLA. Thrombocytopenia, which had never been encountered in this child during the 6-year follow up is a rather unusual manifestation of XLA. However, thrombocytopenia has been reported in XLA. For instance, in a large series of 240 patients in UK, thrombocytopenia was reported in 6. It is believed to be related to autoimmune factors.

The child’s liver dysfunction can be explained by hypoxia and/or sepsis. As the child was on regular IVIG replacement therapy for the past 6 years, transfusion transmissible hepatitis viral infection cannot be ruled out. Renal failure in the terminal phase may have been related to acute tubular necrosis due to septic shock or non-specific glomerulonephritis reported to be associated with XLA. However, I feel that the most likely cause of renal failure in this child was due to IVIG therapy administered on day 2 of admission at the dose of 1 g/kg. IVIG used for replacement therapy contains maltose and sucrose as excipients. Renal failure following IVIG administration when the patient is already in a hypovolaemic state has been described. In one of the largest series, Ilkin and Trujillo described over hundred cases. However, most of their patients were elderly and we have never previously encountered renal failure related to IVIG administration. The various causes of death in patients with XLA have been documented in a large series by Hermazewski and Webster. In this series the commonest cause of death was infection by encapsulated bacteria. Other causes of death included chronic enteroviral infections, notably meningococcal meningitis caused by ECHO virus, malignancies, inflammatory bowel disease and amyloidosis. Invasive fungal and other opportunistic infections were exceedingly rare.

The clinical possibilities in this case are XLA on regular IVIG therapy for the past 6 years, short stature, anaemia, thrombocytopenia, pneumonia, sepsis and renal failure. I would expect the autopsy to find evidence of necrotizing pneumonia, most likely a bacterial pneumonia. I would also expect to see hyaline membrane. Finally, in keeping with a primary diagnosis of XLA, I would expect a paucity of lymph nodes with a distorted architecture along with hypoplastic follicles and germinal centres. The renal failure in this case was most likely due to acute tubular necrosis.

TREATING UNIT’S (DR SURJIT SINGH’S) DIAGNOSIS

**X-linked agammaglobulinaemia with bronchiectasis, pneumonia, sepsis with septic shock and multi-organ dysfunction syndrome**

**CLINICAL DISCUSSION**

**DR VINAY SAKHUJA:** The clinical protocol is now open to the house for comments.

**DR MEENU SINGH:** In a 6-year-old child who presents with bronchiectasis, we would certainly like to rule out other causes of bronchiectasis such as cystic fibrosis, other causes of primary immunodeficiency and structural disorders. In this patient it was ruled out by a normal sweat chloride test. I would also like to see the genetic mutations to be positive for XLA. Hence in the pathology protocol we would be interested in seeing a positive demonstration of the mutations associated with XLA because there are several mutations in cystic fibrosis (about 6 of them described by us), some of which are associated with normal sweat chloride levels at presentation.

The key point in the case is the prolonged IVIG therapy and the child developing thrombocytopenia pre-terminally. I wonder whether in children with primary immunodeficiency, administration of multiple donor-derived IVIG leads to an immune response akin to graft-versus-host disease (GVHD) which can present with multi-organ involvement. The main brunt of the disease seems to be borne by the lungs and the other organs being affected later. Could this be a complication of IVIG therapy?

**DR DHEERAJ GUPTA:** I think in the presence of thrombocytopenia and progressive worsening of lung shadows, alveolar haemorrhage can also be thought of as a contributing factor. A diagnosis of ARDS can be considered even in the presence of diseased lungs on the basis of worsening of the lung shadows and defects in oxygenation.

**DR BIMAN SAIKIA:** DNA samples from the child and his mother were analysed. As Btk gene is a fairly large gene spanning 27 Kb and has 19 exons, we try to screen various exons using Sequence Specific Conformational Polymorphism (SSCP) technique. Abnormal bands were detected in exon 14 of both the mother and the child. This needs to be followed up with DNA sequencing to know the exact mutation. Altered migration pattern was observed in the PCR amplicon from exon 14 compared to the wild-type in both the mother and the child. The sensitivity of mutation detection by SSCP is not more than 95% and it cannot detect homozygous changes or the position of the change. SSCP is a good screening method as it is relatively simple and cheap. However, any variant pattern has to be sequenced to fully characterize the change. So the mere detection of abnormal migration bands does not confirm the presence of a disease causing mutation.

**DR B. R. THAPA:** I wish to focus on the liver function tests during the last admission. We do not know anything about the liver size or consistency before this admission. The serum albumin levels were reduced throughout, indicating that he may have had a chronic liver disease. Markers for hepatitis B and C are not available. His AST was elevated 10-fold and ALT was elevated 3-fold. These indicate a possible underlying chronic liver disease. Two other possibilities include intravenous haemolysis and an acute insult to the liver following ischaemia due to the shock state. However, persistent hypoalbuminaemia should make us suspect an underlying chronic liver disease.
PATHOLOGICAL DISCUSSION

DR. AMANIT BAL: In this young child who was a known case of XLA on regular IVIG, a partial autopsy was performed. The pleural and pericardial cavities were within normal limits but there was 2 L of straw-coloured fluid in the peritoneal cavity.

The thymus weighed about 2 g and showed loss of distinction between the cortex and medulla. There was depletion of lymphoid cells and a few cystically dilated Hassall corpuscles and areas of fat infiltration indicating age-related involution.

The hilar, carinal, mediastinal, peripancreatic and para-aortic groups of lymph nodes were enlarged. The mediastinal nodes measured about 1–3.5 cm in diameter and were greyish-brown in colour. On microscopic examination, there was absence of primary and secondary lymphoid follicles. The T-zone areas and sinuses were normal. This was confirmed on immunostaining with CD3 (T-cell marker) and CD20 (B-cell marker) (Fig. 1). In addition there was expansion of the subcapsular sinuses and sinusoidal areas which showed marked capillary proliferation lined by plump endothelial cells and contained red blood cells (Fig. 2a). These changes of nodal angiomatosis were highlighted by CD31 immunostain, which is an endothelial marker (Fig. 2b).

In addition, a few large haemorrhagic areas were seen in the lymph node parenchyma.

The spleen showed complete absence of the white pulp and the intestine showed presence of diffuse lymphoid cells but the Peyer’s patches were absent.

The lungs weighed 750 g and were solid and heavy. The left lower lobe was absent because of previous lobectomy, the pleura showed fibrinous pleuritis. The trachea showed mild mucosal congestion. On cut section the right lower lobe showed dilated bronchi extending up to the pleural surface. The walls of the bronchi were thickened and the lumen contained impacted secretions (Fig. 3A). There was diffuse bilateral haemorrhagic consolidation, and focal greyish-white areas of consolidation in the peribronchiolar regions. The hilar lymph nodes were enlarged measuring 1–2 cm in diameter. On microscopic examination the dilated bronchi showed ulceration of the lining epithelium which was replaced by granulation tissue, and moderate lymphomononuclear cell infiltration (Fig. 3B). The focal areas of squamous metaplasia of lining epithelium and osseous metaplasia of the bronchial cartilage were noted. The blood vessels showed marked medial hypertrophy and fibro-intimal proliferation better highlighted on an EVG stain. The surrounding lung parenchyma showed fibrosis, adenomatoid change, focal necrotizing pneumonia, patchy diffuse alveolar damage (Fig. 3C) and extensive intra-alveolar haemorrhage (Fig. 3D). All these morphological changes in the lungs were overshadowed by the intra-alveolar haemorrhages.

The liver weighed 900 g and was firm and slightly enlarged. Its capsular surface was smooth with no nodularity and the cut section showed exaggerated mottling. The portal vein, biliary tree and inferior vena cava were normal. On microscopic examination the hepatic architecture was preserved, there was sinusoidal dilatation and centrilobular haemorrhagic necrosis.

The pancreas had normal acini and islets of Langerhans. There was no evidence of acute or chronic pancreatitis.

The spleen weighed 140 g. The capsule was thickened, and on

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**Fig 1.** A: Gross photograph of the enlarged mediastinal group of lymph nodes; B: photomicrograph showing the complete absence of lymphoid follicles, however, the T-zone areas and sinusoids were normal (H&E, ×100); C: photomicrograph showing CD3 (T-cell marker) positive T-zone; D: photomicrograph showing absence of CD 20 (B-cell marker) cells indicating B zone depletion

**Fig 2a.** Photomicrograph showing expansion of the subcapsular sinuses and sinusoidal areas by marked capillary proliferation (H&E, ×100)

**Fig 2b.** Photomicrograph showing capillary-sized blood vessels lined by plump endothelial cells and the contained red blood cells (H&E, ×200). These changes of nodal angiomatosis are highlighted by CD31 immunostain (an endothelial marker)
cut section most of the parenchyma was infarcted with a preserved rim at the periphery. There were multiple nodular haemorrhagic lesions of approximately 0.8–1 cm diameter scattered throughout the splenic parenchyma (Fig. 4a and 4b). A splenunculus measuring 2.5 cm in diameter was present which also showed infarction of the parenchyma. On microscopic examination the main splenic vein at the hilum and the trabecular branches showed exuberant intravascular papillary endothelial hyperplasia, at places intimately associated with a thrombus (Fig. 5). These papillary tufts were fully endothelialized, as highlighted by the CD31 immunostain, and the core of these papillae contained red blood cells, platelets and fibrin (Fig. 6). There were large areas of coagulative necrosis with haemorrhagic borders indicating stasis infarction (Fig. 7). The infarcted area showed fresh thrombi in the trabecular splenic veins.

Intravascular papillary endothelial hyperplasia (Masson’s haemangioma) is characterized by exuberant endothelial proliferation within the lumen of the medium-sized veins and is considered to be a reactive vascular proliferation. They have a propensity to occur in the head, neck, fingers and trunk. However, occurrence within the abdominal cavity is rare, and is especially rare in the spleen. There is a case report of intravascular papillary endothelial hyperplasia (Masson’s haemangioma) in the liver, but I could not find any case report of this entity in the spleen. Primary hypogammaglobulinaemia has been associated with different vascular malformations. Kasabach–Merritt syndrome (KMS) is a combination of haemangioma, thrombocytopenia and coagulopathy. In this syndrome, local activation of coagulation commonly results in consumption coagulopathy. The haemangioma may be superficial or within a visceral organ; when no cutaneous haemangioma is present, one must search for haemangiomas located in the viscera such as spleen, liver or brain. Neither the site nor the size of the haemangioma reliably predicts the development of KMS. Thrombocytopenia is often severe (<50 000 platelets/cmm) and results in visceral haemorrhages or purpura. Cardiovascular compromise or collapse, petechiae and bleeding may mimic acute overwhelming sepsis and mortality as a result of uncontrollable haemorrhage.
section there was medullary congestion with a distinct cortico-medullary junction. On microscopic examination the proximal tubules showed shedding of the lining epithelial cells and the lumen contained granular casts indicating acute tubular necrosis. The distal tubules contained faintly PAS-positive fractured casts with a minimal tubular epithelial reaction. These casts showed crystalline structure on Masson’s trichrome stain (Fig. 10). A single focus of distal tubules showed the presence of yeast and pseudohyphae of Candida. The glomeruli, blood vessels and interstitium were within normal limits.

As the patient had received a dose of IVIG a day before acute renal failure, we looked for evidence of a probable role of exogenous immunoglobulin in its causation. The potential mechanisms of acute renal insufficiency induced by IVIG include:

1. Tubular obstruction from proximal renal tubular cell swelling secondary to sucrose nephropathy;
2. Ischaemia secondary to renal artery vasoconstriction (which was seen in this case as acute tubular necrosis); and
3. Deposition of immune complexes in the glomerulus or interstitium.

There are case reports of KMS being associated with diffuse splenic and pancreatic haemangiomatosis and intracranial Masson’s haemangiomas.

**Gastrointestinal tract:** The upper and middle third of the oesophagus, and stomach showed superficial mucosal haemorrhages (Fig. 8). The small intestine showed three large patches of transmural haemorrhage (Fig. 9). Microscopic examination showed areas of mucosal, submucosal and serosal haemorrhage with haematoma formation in the intestinal serosa.

The heart weighed 187 g, was grossly enlarged and globular, with biventricular dilatation, the right ventricle wall thickness was 0.6 cm and the left ventricle wall thickness was 1.2 cm. There were subendocardial haemorrhages and brownish discoloration of the ventricular walls. The valves were normal and no vegetations were seen. Microscopic examination revealed multiple foci of myocyte necrosis, interstitial oedema and haemorrhage indicating terminal ischaemic changes. The coronary arteries showed no occlusion.

The kidneys together weighed 300 g, were swollen and had pin-head size haemorrhages on their external surface. On cut
However, no study has reported the appearance of casts within epithelial reaction resembling cast nephropathy in response to exogeneous immunoglobulins.

Bone marrow: was normocellular with adequate megakaryocytes and relative erythroid hyperplasia

FINAL DIAGNOSIS

In a 12-year-old boy who was a known case of X-linked agammaglobulinaemia

— B-zone depletion in lymphoid organs
— Bronchiectasis, necrotizing pneumonia, diffuse alveolar damage and extensive pulmonary haemorrhage
— Intravascular papillary endothelial hyperplasia (Masson’s haemangioma) of the splenic vein leading to splenic infarct and Kasabach–Merritt syndrome
— Nodal angiomatosis
— Severe acute tubular necrosis and focal fractured casts with reaction possibly secondary to exogeneous immunoglobulins
— Myocardial ischaemia

CONCLUDING DISCUSSION

Dr Vinay Sakhuja: Whereas we have some explanation for the thrombocytopenia, elevated liver enzymes remain unexplained.

Dr Pankaj Malhotra: Thrombocytopenia is possibly due to disseminated intravascular coagulation (DIC) and sepsis rather than to KMS. All haemangiomatous disorders such as Masson’s haemangioma, Blue Rubber Nevus syndrome and other haemangiomas produce some degree of thrombocytopenia. Since the patient had undergone an uneventful lobectomy, thrombocytopenia was most likely of recent origin. If this is the case, prolongation of partial thromboplastin time with Kaolin/activated partial thromboplastin time and thrombocytopenia are related to the DIC and sepsis rather than Masson’s haemangioma. There was only one small haemangioma.

Dr B. R. Thapa: The liver showed centrilobular congestion and sinusoidal dilatation. What was the status of the central veins? A small haemangioma in the spleen cannot explain thrombocytopenia, DIC and coagulopathy. Was there any evidence of thrombosis of the central or hepatic veins, which could explain the deranged liver function?

Dr Amanjit Bal: There were no thrombi in the central or hepatic veins, haemangiomomas in the liver or features to suggest chronic liver disease. The findings in the liver are suggestive of terminal ischaemic changes. All haemangiomas do not present with thrombocytopenia. Only when multiple and enlarging, do these entrap platelets leading to thrombocytopenia. DIC must have contributed to thrombocytopenia, but at the time of autopsy, pneumonia or sepsis were not severe enough to explain DIC.

REFERENCES


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