Peliosis Hepatis following treatment with androgen-steroids in patients with bone marrow failure syndromes

Androgens widely used in the treatment of bone marrow failure syndromes can in rare cases cause hepatic peliosis, a pathological entity characterized by multiple blood-filled cavities in the liver parenchyma. Bone marrow failure syndromes per se are associated with a low coagulation status, which is further magnified by bone marrow transplantation for aplastic anaemia due to deep thrombocytopenia. Both these conditions can cause bleeding; their combination is especially dangerous. We describe two cases of aplastic anaemia due to paroxysmal nocturnal hemoglobinuria and Fanconi syndrome, in which patients developed peliosis hepatis after prolonged treatment with androgens. One patient developed severe subcapsular bleeding, successfully treated with catheterization of the right hepatic artery and embolization of the bleeding site. The second patient bridged over deep post-transplant aplasia with high frequency platelet transfusions, and demonstrated an uncomplicated post-BMT course. We suggest avoiding or interrupting treatment with androgens in patients preparing for BMT.

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Androgen-steroids have been commonly used in the past for treating patients with bone marrow failure syndromes.[1] Development of more effective treatment modalities such as growth factors, immunosuppressive agents, and stem cell transplantation has largely displaced androgens from the therapeutic armamentarium.

Patients receiving prolonged treatment with androgens face an increased risk of developing hepatic tumours, most of which appear to be benign-such as adenomas and peliosis. Such benign hepatic tumours are usually androgen-dependent, and generally decrease in size after cessation of treatment.[2,3] Peliosis is a pathological entity characterized by multiple blood-filled cavities, mostly involving the liver (peliosis hepatis). Peliosis hepatis is uncommon; however, it is one of the most serious complications associated with the use of androgen-steroids.[4,5]

In the present article, we report our experience involving 2 patients with bone marrow failure syndromes (Fanconi Anaemia and paroxysmal nocturnal hemoglobinuria) who developed peliosis hepatis following androgen-steroid treatment.

Patients and methods

Case 1. A twenty-nine-year-old male was admitted to our Department for allogeneic stem cell transplantation due to paroxysmal nocturnal hemoglobinuria diagnosed 9 years earlier. At diagnosis, the patient suffered from general weakness, dark-coloured urine in the morning, hyperbilirubinemia, hemolytic anemia and a pancytopenic tendency. Bone marrow biopsy performed at diagnosis demonstrated hypercellularity with erythroid hyperplasia. CD55 and CD59 on erythrocytes were negative. The patient was treated with Danasol which provided a good response, and required no blood product support.

Routine abdominal US performed in October 2003 revealed several hypoechogenic hepatic lesions suspicious for hepatic adenomas. Androgen treatment was discontinued. Seven months later, an abdominal US showed the same lesions, which remained unchanged; however, the patient's pancytopenia worsened. Bone marrow sampling at that time was hypocellular and the patient received red blood packed cells and platelet support for the first time during the course of his disease. A therapeutic decision was made to perform allogeneic stem cell transplantation from a fully matched sister. On admission for BMT, in October 2004, the patient was pale but otherwise had a normal physical exam, including normal liver and spleen sizes. Conditioning regimen included fludarabine 30 mg/m^2/day for 6 days, cyclophosphamide 60 mg/m^2/day for 2 days and thymoglobulin® (IMITIX, Sangstat, Lyon, France) 2.5 mg/kg/day for 4 days. Graft-versus-host disease (GVHD) prophylaxis included cyclosporine, 3 mg/kg/day from day -4. On the days of transplantation, he received 30.6x10^8 total nuclear cells (TNC), without complications. Engraftment of absolute neutrophil count (ANC)>0.5x10^9 per L and platelets>50x10^9 per L was achieved on days +11 and +15, respectively.

On day +9 following transplantation, when the platelet level dropped to 21x10^9 per L, the patient developed acute severe abdominal pain-initially, peri-umbilical and masked by pre-existing pains due to chemotherapy. In due course, the pain became more severe and localized in the upper right abdominal quadrant. Several hours later, the patient developed an all-encompassing clinical picture of hemorrhagic shock: haemoglobin dropped from 8.9 to 4.9 g/dL; blood pressure 80/30 mm Hg; the patient suffered from sweating, dizziness, tachycardia. Abdominal and pelvic computed tomography (CT) was performed, revealing multiple hypervascular lesions in both lobes of the liver - a typical picture of *peliosis hepatis*, with a large subcupsular liver haematoma. The origin of the haematoma was identified as a 7.5 cm well-defined round hyperdense lesion in the right lobe of the liver (Figure 1). Free intraperitoneal fluid was also noted in the abdomen. The patient was transferred to the angiography unit for urgent catheterization of the right hepatic artery (which originated from the superior mesenteric artery as shown in Figure 2a). Embolisation of segments 7 and 8 of the liver was performed by selective injection of 500 Units of PVA particles (Figure 2b). Hemodynamic stability and hemostasis were achieved. Following the procedure, the patient was febrile with fever up to 40°C for an entire month. Repeat blood, urine and throat cultures were negative. The fever was diagnosed as related to the large intrabdominal haematoma, and antibiotics were discontinued

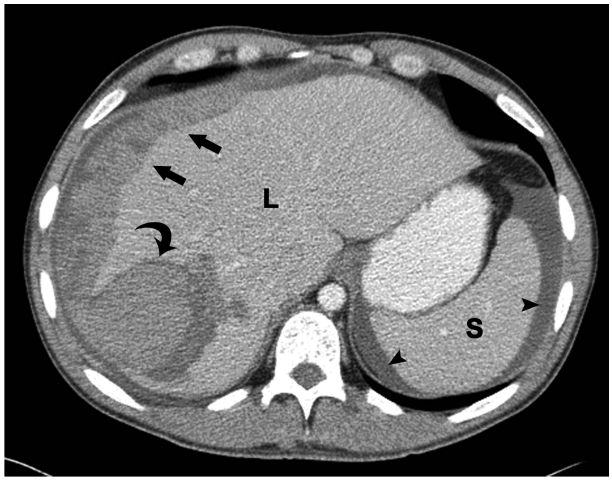

Figure 1. Patient #1 ten days following BMT. The patient developed severe upper right abdominal pain and hemorrhagic shock. Abdominal CT demonstrates a 7.5 cm hyperdense mass in segment 7 of the liver (curved arrow). A large subcapsular haematoma surrounds the liver (arrows), originating from this lesion. The mass and the subcapsular collection are hyperdense, representing acute blood. Free intraperitoneal fluid is noted around the spleen (arrowheads). L=liver; S=spleen

shortly after engraftment. No additional significant complications were encountered during the patient's hospitalization. He was discharged on the 34th day following transplantation, in a good clinical condition.

Routine ambulatory follow-up was performed in the day-care unit, without complications. A follow-up CT 4 months after the acute episode of bleeding demonstrated near-complete resolution of the subcapsular haematoma of the liver, as well as a reduction in the size of the hepatic lesion in segment 7 (Figure 3). No signs of GVHD or any other complications have been documented to date (two years post transplantation); the patient is fully rehabilitated haematologically as well as physically.

Case 2. An eleven-year-old female patient was referred to our department with aplasia due to Fanconi's anaemia (FA). She had been diagnosed with FA at the age of 5 years. Initially, she presented with anaemia (Hb 86 g/L) and a mild decrease in the platelet count (<100x10^9 per L). A diepoxybutane test was positive; subsequent molecular diagnosis revealed mutations responsible for complementation group A: mutations in gene FAA on chromosome 16q24.3: a) missense mutation at position 2: Met^{1}Lys (ATG>AAG) in exon 1 and b) frameshift mutation in exon 2: 14 basepair deletion (del 119-132 CACAGAAATTAAAG, previously not listed in the FA database).

One year after the diagnosis was established, the patient began treatment with oxymetholone, with a good initial response. Two years after initiation of this treatment, liver enlargement was noted, with abnormal liver function tests on blood chemistry. A 3-4 fold rise was noted in bilirubin levels (64 mmol/L), with a mild increase of transaminase levels. Oxymetholone therapy

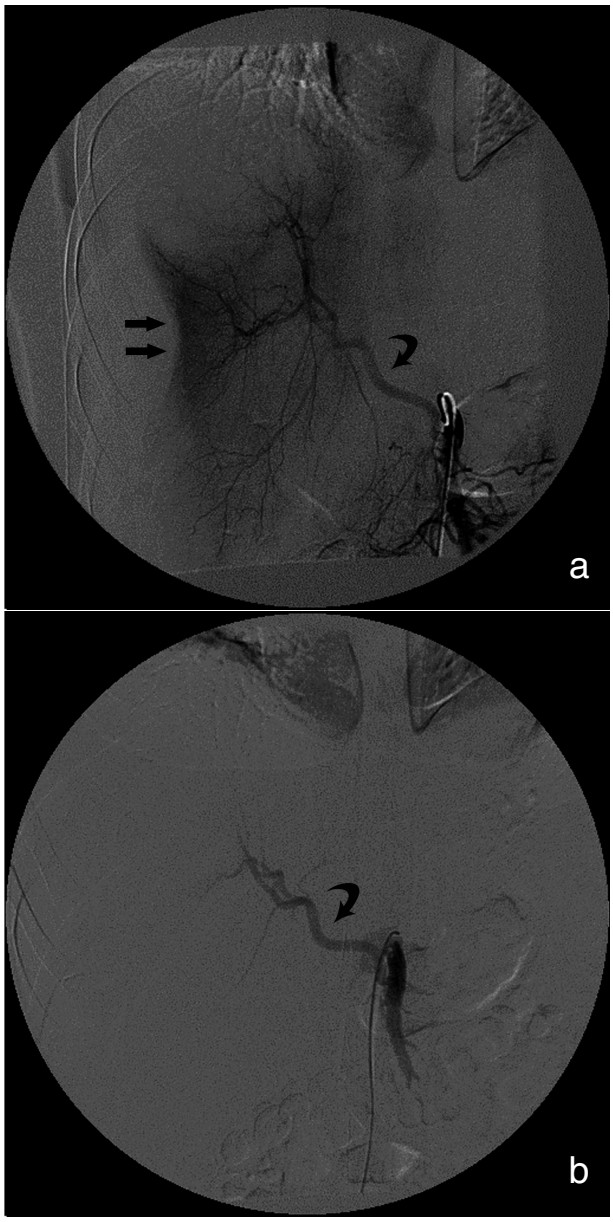

Figure 2. Urgent angiography performed in patient #1 at the time of abdominal pain. Selective injection into the right Hepatic artery (curved arrow) demonstrates the vasculature of the right lobe of the liver (a). The origin of the right Hepatic artery is displaced, originating from the superior mesenteric artery. A large subcapsular hematoma is depicted as medial deviation of the lateral border of the liver from the chest wall (arrows). Successful embolization of segments 7 and 8 of the liver (b) was performed with complete devascularization of the segmental arteries coming off the right Hepatic artery (curved arrow).

was continued for an additional year, until the patient developed pancytopenia (WBC 1.7x10^9/L with single granulocytes in blood smears, minimal Hb 6.2 g/L, platelets 40 then 20x10^9/L). The patient also experienced general deterioration, purpura, and a few episodes of fever of unknown origin (FUO). The patient's family were referred to our centre, MUD was found and BMT was performed after conditioning with i.v. fludarabine 30 mg/m^2/day for 6 days; i.v. cyclophosphamide 5 mg/kg/day for 2 days; i.v. busulfex 3.2

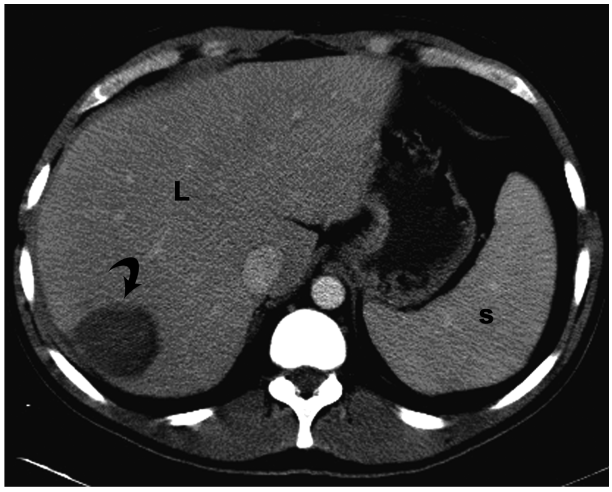

Figure 3. Patient #1 four months following embolization. Abdominal CT demonstrates near complete resolution of the subcapsular hematoma of the liver, as well as reduction in the size of the segment 7 hepatic lesion (curved arrow). L=liver; S=spleen

mg/kg/day for 2 days; anti-thymocytic globulin (ATG, Fresenius, Schering, AG) 10 mg/kg/day for 4 days. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine (CSA) in i.v. dose 3 mg/kg daily in two divided doses starting on day –4 with control of blood levels. Once the patient was engrafted, CSA was administered orally in an equivalent dose.

Oxymetholone was discontinued on admission, before conditioning was initiated, 10 days before transplant. Liver tests at that time were as follows: bilirubin 41-76 mcmol/L (2-4-fold increase above normal levels), AST was 78-179 (2-5 times as high as normal), ALT 143-253 units (3-5 times as high as normal), GGTP 110-149 units (1.5-2 as high as normal). To further investigate these liver abnormalities, an abdominal CT was performed, demonstrating multiple liver lesions spread throughout both lobes of the liver. These lesions differed in size and attenuation, some of them hypervascular on dynamic imaging (Figure 4 a-b). The CT pattern was classic for *peliosis hepatis*, and the diagnosis was established accordingly.

Following our experience with patient #1 (described above) that developed a massive haemorrhage from his hepatic lesion, we kept the girl on higher platelet levels than standard (from 50 to 70x10^9/L). The patient successfully engrafted platelets on day +14, and since that time has had stable donor chimerism.

On follow-up, the patient developed ITP three months after BMT, with platelet levels dropping acutely within 3-4 days. The diagnosis was based on the presence of large platelets in the peripheral blood smears. The patient received high dose IVIG (0.4 g/kg for 5 consecutive days, total dose 2 g/kg) with an excellent response, and remained stable thereafter. Following discontinuation of Oxymetholone, liver function tests normalized (Figure 5). Follow-up CT performed 6 months after the initial CT demonstrated significant resolution

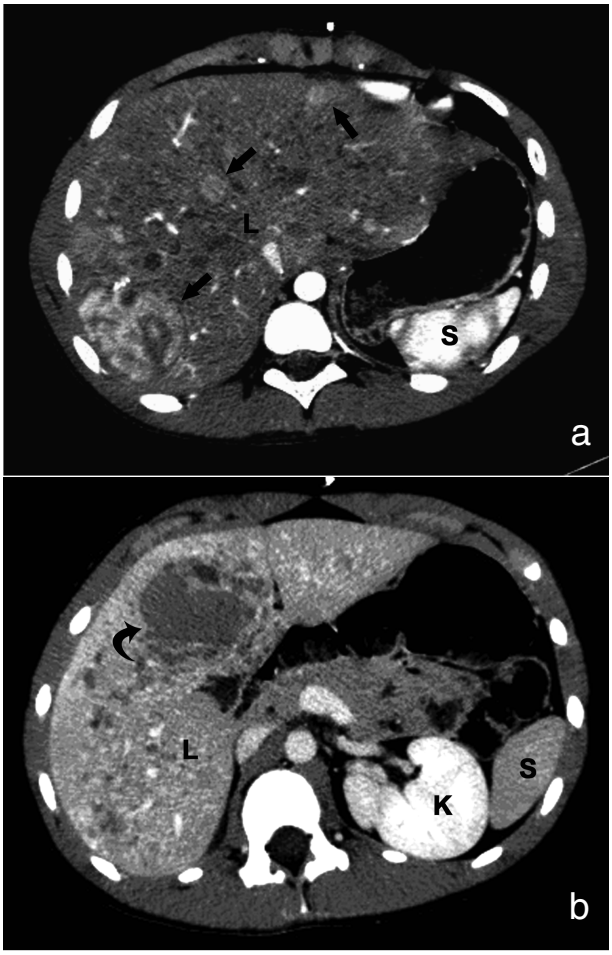

Figure 4. Patient #2 ten days prior to BMT, presenting with abnormal liver function tests. Contrast enhanced abdominal CT at an arterial phase (a) demonstrates multiple hypervascular hepatic lesions (arrows). An additional image at a lower level (b) demonstrates a large hypodense hepatic lesion (curved arrow). Similar smaller lesions are dispersed throughout the liver. L=liver; S=spleen; K= kidney.

of the hepatic lesions, with a single residual lesion in segment 7 of the liver (Figure 6).

Discussion

Peliosis is a pathological entity characterized by multiple cyst-like, blood-filled cavities within parenchymatous organs, mainly the liver and spleen.[6] Peliosis has been reported to be associated with long-term treatment with steroids, oral contraceptives, tamoxifen, estrogens, intravenous drug abuse and chronic alcoholism.[7,8] It has also been associated with malignancies, solid organ transplantation and chronic infections, infection with *Bartonella henselae* or *quintana* in immunocompromised patients.[9-14] In 20%-50% of cases, no associated condition is identified[15]

Pathologic anatomy. In the liver, at gross inspection, the peliotic lesions give the cut sections a *Swiss cheese* appearance. Peliosis is characterized by blood-filled distension of hepatic sinusoids ranging from 2 mm to 5 cm.

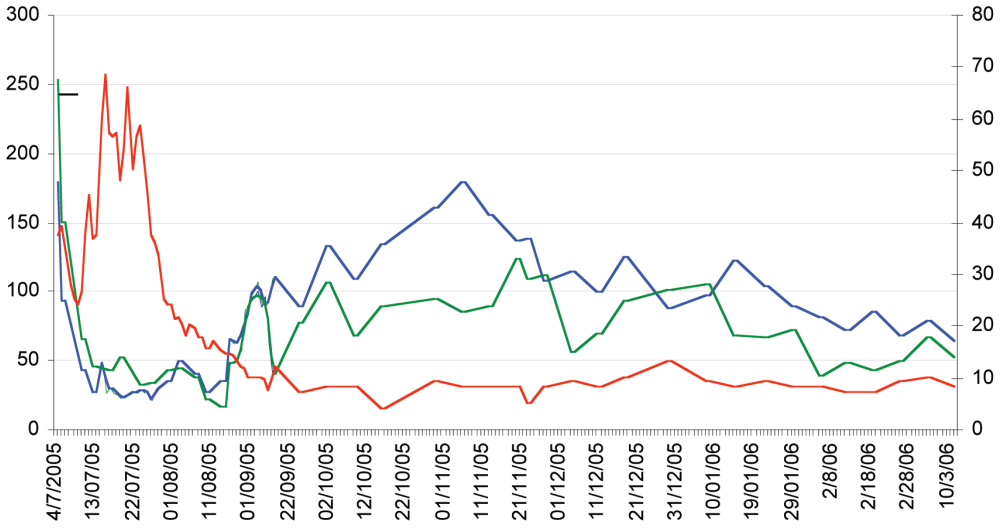

Figure 5. Patient #2, changes in liver test after discontinuation of treatment with androgens. Red: total bilirubin (µmol/L), blue: AST, green: ALT (U/L); — day of BMT.

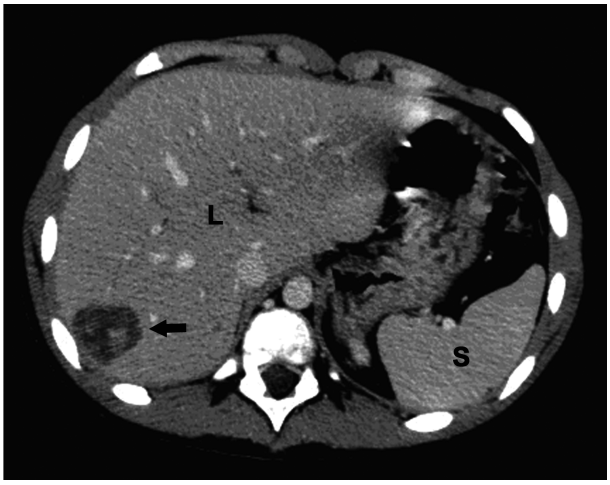

Figure 6. Follow-up abdominal CT in patient #2 six months after the first CT scan demonstrates significant resolution of the hepatic lesions with a single residual lesion in segment 7 of the liver (arrow). The lesion shows internal enhancement, depicting its vascular nature. L=liver; S=spleen

Microscopically, two different types of peliosis can be distinguished: a) *parenchymal peliosis* consisting of irregular cavities that are neither lined by sinusoidal cells nor by fibrous tissue, and b) *phlebectatic peliosis* characterized by regular, spherical cavities lined by endothelium and/or fibrosis.[16]

Pathogenesis. Acquired malformation of the sinusoidal system may be triggered by altered local intravascular pressure conditions, toxic substances, or active proliferation of endothelial cells.[15] Proliferation of endothelial cells in turn can be triggered by angiogenetic factors; *Bartonella* is thought to be relatively unique among bacteria in inducing such factors.[14,17,18]

Differential diagnosis can prove to be a difficult task: haemangiomas, hepatic abscesses, haematomas, and primary or metastatic tumours, as well as secondary hepatic congestion due to veno-occlusive disease or the Budd-Chiari syndrome[19,20] need to be ruled out. The CT appearance of hepatic peliosis can range from no visible abnormality, to multiple lesions of varying sizes and attenuation.[10,21] Small cavities may not be visible on CT. Cavities, which communicate with sinusoids, are often filled with blood and may be hyperdense on non-contrast enhanced CT, and will enhance in a fashion similar to portal blood vessels. Such a lesion is demonstrated in patient #1. Thrombosed cavities may appear as low attenuation lesions during all phases of contrast enhancement. A multiple lesion appearance is demonstrated in patient #2. If clinical and radiological features are suggestive of peliosis, withdrawal of the causative drug and/or *wait and watch* policy is recommended. Percutaneous liver biopsy should be avoided because of the significant risk of severe bleeding.[22]

Clinical course and treatment. Clinical presentation may range from asymptomatic to progressive cases with liver failure or fatal spontaneous intrabdominal haemorrhage.[23,24] When an infectious pathogen (e.g. *Bartonella*) is considered the etiological agent, appropriate antibiotic treatment may lead to complete resolution of peliosis.[13] In cases of liver rupture and intrabdominal bleeding, transarterial embolization is reported as an effective treatment.[25] Rare reports of liver transplantation due to generalized extensive peliosis are described in English language publications.[22,26]

Conclusions

Many patients suffering from bone marrow failure syndromes receive androgens before transplantation. Our opinion is that treatment with androgens must be avoided if the patient is a candidate for BMT, in similarity with the practice for blood product transfusions. In case androgen treatment has already commenced, close

liver monitoring is required with subsequent follow-up. Androgen treatment must be stopped immediately after the decision is made to perform BMT, as changes may be reversible within the few months leading up to the transplantation (e.g., during donor search). If lesions are discovered that may present a life-threatening condition, the patient is to be maintained in a good coagulation status.

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