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REVIEW /*Pediatric imaging*

Imaging features of atypical bleeds in young patients with hemophilia

M. Gavrel[a,*], **A. Rafowicz**[b], **R. d'Oiron**[b], **S. Franchi-Abella**[a], **T. Lambert**[b], **C. Adamsbaum**[a,c]

[a] *Pediatric Radiology Department, Hôpitaux Universitaires Paris-Sud, Bicêtre AP—HP, 94270 Le Kremlin-Bicêtre, France*
[b] *Reference Centre for Hemophilia and Hemorrhagic Constitutional Diseases, Hôpitaux Universitaires Paris-Sud, Bicêtre AP—HP, 94270 Le Kremlin-Bicêtre, France*
[c] *Faculty of Medicine, Paris-Sud University, 94270 Le Kremlin-Bicêtre, France*

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Abstract Hemarthroses and muscle bleeds are well-known and well-documented complications in pediatric and young adult hemophilia patients. In contrast, deep bleeds in atypical locations can be a diagnostic challenge, since clinicians and radiologists are often unfamiliar with their clinical and radiological features. Some atypical bleeds, however, can be life-threatening or severely disabling, highlighting the need for prompt, accurate diagnosis. Rare bleeds include central nervous system bleeds (including intracranial and spinal hematomas), urogenital bleeds, intra-abdominal bleeds (mesenteric and gastrointestinal wall hematomas) and pseudo tumors in unusual locations like the sinonasal cavities. Because clinical assessment can be difficult, clinicians and radiologists should be aware of the possibility of these rare complications in their hemophilia patients, so that they can avoid unnecessary invasive diagnostic and surgical procedures and institute prompt, appropriate treatment. The purpose of this review is to illustrate the imaging features of bleeds that occur in rare locations in young (i.e., children and young adults) patients with hemophilia to make the reader more familiar with these conditions.

* Corresponding author.
E-mail address: gavrelmarie@gmail.com (M. Gavrel).

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Hemarthroses and muscle bleeds are well-known complications in pediatric and young adult hemophilia patients. On the opposite, deep bleeds in atypical locations can be a diagnostic challenge, since clinicians and radiologists are often not familiar with the clinical and radiological features of these entities. Such bleeds may be life-threatening and require immediate and/or prolonged treatment. Some of them may mimic surgical emergencies or malignancies, resulting in unnecessary biopsies or invasive procedures when conservative management with factor replacement therapy alone would have been appropriate. A potentially serious complication of recurrent soft tissue hemorrhage is the gradual development of hemophilic pseudotumors, which can compress nearby neural or vascular structures. In these contexts, imaging is an invaluable aid to appropriate diagnosis.

The purpose of this review is to illustrate the imaging features of bleeds that occur in rare locations in young (i.e., children and young adults) patients with hemophilia to make the reader more familiar with these conditions. Hemarthroses and muscle hematomas, which are frequent and well-known complications, will not be addressed in this article.

Central nervous system hemorrhage

Intracranial hemorrhage

The incidence of central nervous system bleeding in hemophilic patients ranges from 3 to 8.7%, with more than half occurring in very young patients [1,2]. Prompt and accurate diagnosis is essential to initiate rapid treatment and reduce the risk of sequelae. The incidence of intracranial hemorrhage in neonates with hemophilia is between 3 and 4%, and birth trauma is the leading cause [2—4]. Diagnosis may be delayed when there is no known family history of hemophilia [5].

The most common symptoms of intracranial hemorrhage in early childhood include sudden increase in head circumference, apathy, behavioral changes, seizures with or without fever (Fig. 1), vomiting, and coma. Clinical neurological examination may be normal. Headaches and motor dysfunction have also been reported in children older than 2 years [6].

Magnetic resonance imaging (MRI) or computed tomography (CT) can be used to localize the intracranial hemorrhage, which may be intraparenchymal, subdural, and/or subarachnoid. Intraventricular and epidural hematomas are less frequent. Several sites of bleeding are frequently involved. Ultrasound is not sensitive enough to reveal intracranial hemorrhage in neonates, particularly when it occurs in the posterior fossa [7]. The presence of several sites of bleeding and a history of minor trauma in a child should raise the possibility of hemophilia.

Beyond the perinatal period, a major differential diagnosis is abusive head trauma. In abusive head trauma, however, clots at the convexity, when present, are due to ruptured bridging veins, thus indicating violent acceleration-deceleration trauma [8].

Acute spinal hematoma

Intraspinal bleeding in hemophilia patients is very rare, representing only 2 to 8% of CNS hemorrhages [9,10]. Spontaneous spinal epidural hematomas (SSEHs) are believed to have a venous origin, caused by the rupture of veins in the valveless epidural venous plexus when abdominal pressure increases (e.g., after sneezing or coughing). They can also occur after lumbar puncture in patients not known to have hemophilia who are not given clotting factor concentrates prophylactically. SSEHs are usually confined to the posterior epidural space (Fig. 2), while anterior epidural hematomas are rare [11]. Spinal subdural hematomas are even more rare, and reported only twice to date [12,13]. The most common location for SSEHs is the cervicothoracic spine (> 40% of cases), followed by the thoracic spine and cervical spine. Lumbar spinal hematomas are less common [14].

SSEHs typically present as acute back pain combined with a sensorimotor neurological deficit and radicular pain. It is important to note that neurological symptoms may be absent; irritability and refusal to stand up, walk, sit, or lay down may be the only symptoms at onset, and should prompt immediate MRI examination. Spine stiffness, in particular, should alert the clinician to the possibility of an SSEH. These potential early signs often precede the onset of neurological deficits by several hours or days. The prognosis is directly related to the mass effect on the spinal cord.

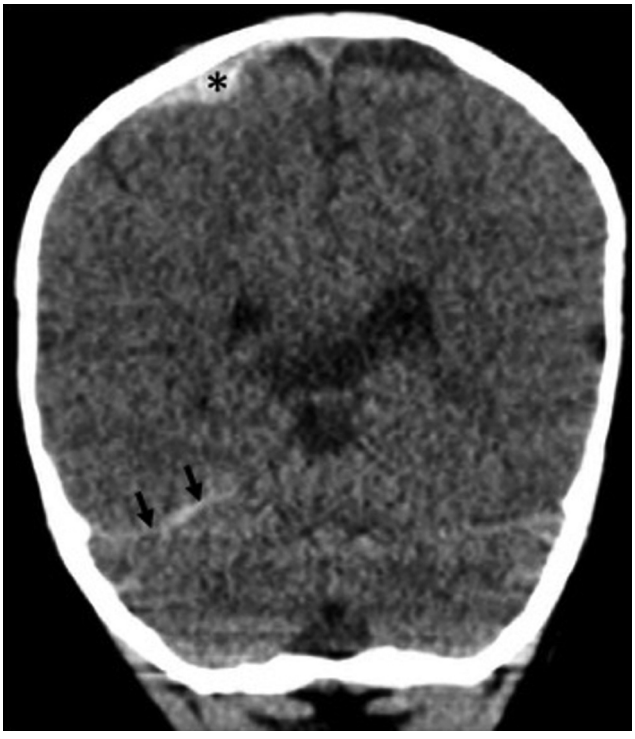

Figure 1. 26-month-old boy with severe hemophilia A. Unenhanced head CT in the coronal plane shows extra-axial hematoma (asterisk) and a subdural hematoma of the tentorium (arrows). This child presented with partial febrile seizures (38.5 °C) and a normal neurological examination between seizure episodes. Head trauma two days earlier was reported.

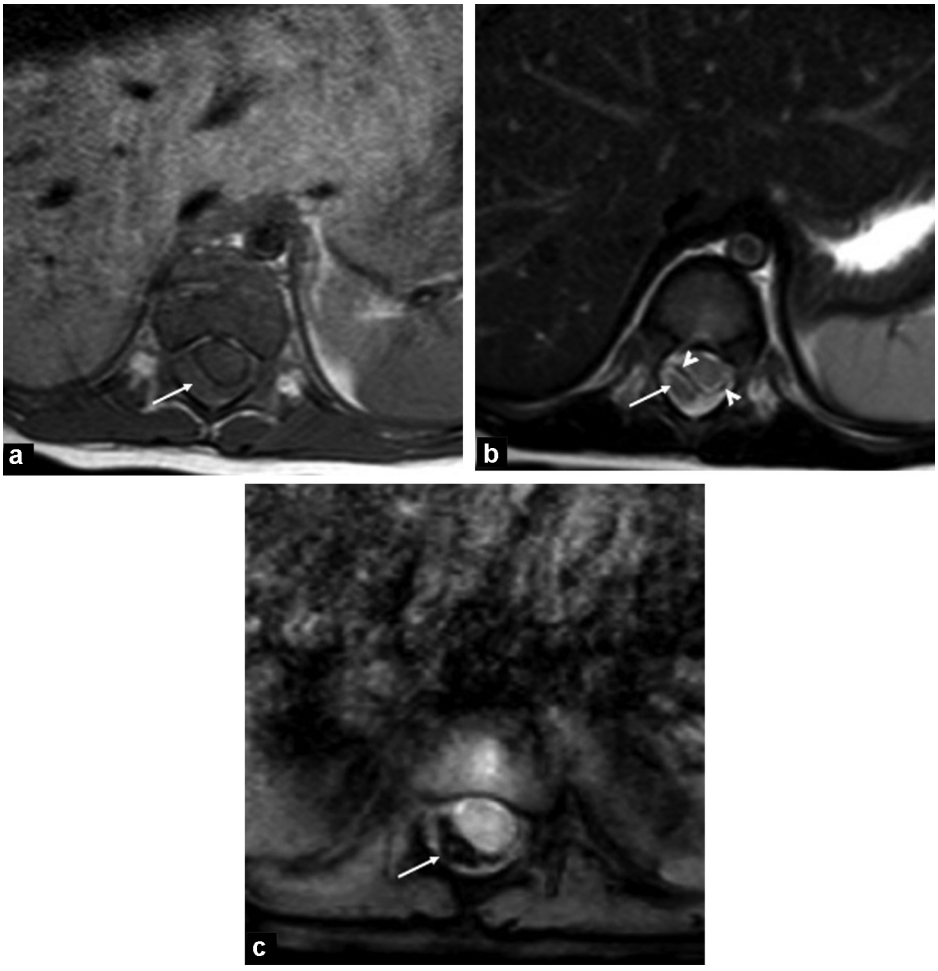

Figure 2. 13-month-old boy with severe hemophilia A presenting with acute abdominal pain, refusal to stand up, and no history of trauma. T1-weighted (A), T2-weighted (B) and T2-weighted fat-suppressed spoiled gradient-echo (C) MR images in the transverse plane show spontaneous spinal epidural hematoma (arrows) in the posterior epidural space. The thin line corresponding to the dura mater (arrowheads on B) is displaced anteriorly.

Subdural hematomas present with similar clinical signs but have a less fulminant clinical course.

An SSEH appears as a biconvex mass displacing the spinal cord anteriorly (Fig. 2). Acute hematoma is isointense on T1-weighted images and hyperintense on T2-weighted images. The very low signal of the deoxyhemoglobin, appearing after several hours, is better seen on T2-weighted spoiled gradient-echo sequences (Fig. 2).

In the absence of cord compression, clotting factor concentrates may be given as a single treatment with a close follow-up. Nevertheless, most SSEH require urgent operative decompression [15]. Intraspinal bleeding is rare in children with no hemophilia, and can also be due to a vascular malformation or trauma, including from abuse. Differential diagnosis of an intraspinal mass in a child, which includes lymphoma, metastasis, schwannoma, and abscess, may delay the diagnosis in infants with previously undiagnosed hemophilia [16].

Urogenital hemorrhage

Ureteral hemorrhage

Spontaneous submucosal intramural hemorrhage that dissects the ureter is a rare complication of hemophilia. Only a few cases have been reported in children [17—19]. The symptoms can include nonspecific abdominal pain [17,18], vomiting, and macroscopic or microscopic hematuria, which is frequently missed [18]. Interestingly, in anticoagulated adults with ureteral wall bleeding, it can take 72 hours after the onset of the symptoms for hematuria to occur [20].

On ultrasound, an intramural ureteral bleed may be misinterpreted as an iliopsoas hematoma. Indeed, ultrasound may show a hyperechoic, retroperitoneal hematoma and unilateral dilatation of the renal pelvis [18]. Moreover, the psoas muscle may be enlarged due to extravasation of the

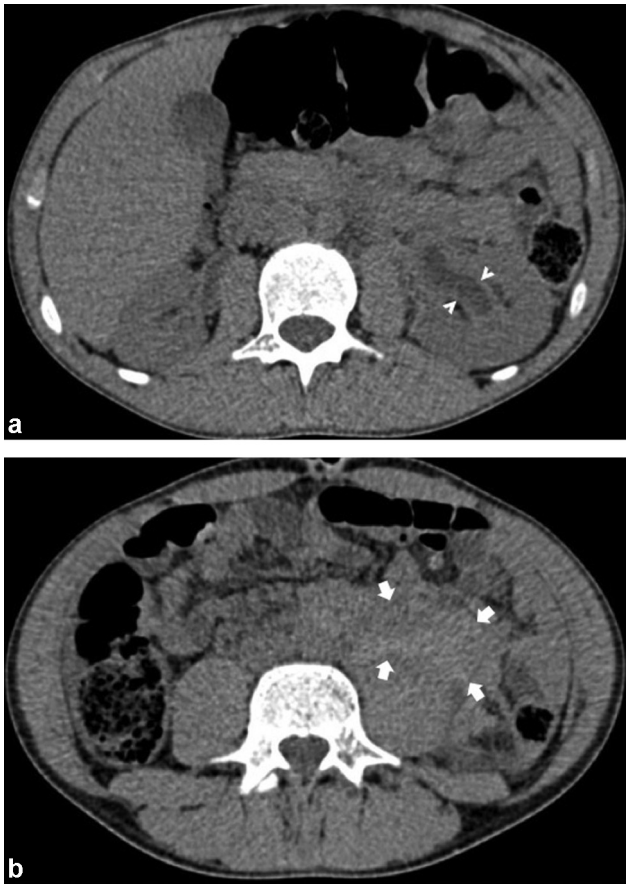

Figure 3. 17-year-old boy with severe hemophilia A presenting with acute left flank pain and negative hematuria. Unenhanced abdominal CT images in the transverse plane (A and B) show a left ureteral hematoma as a spontaneously hyperattenuating thickening of the left renal pelvis (arrowheads on A) and a left retroperitoneal hematoma (arrows on B) extending in front of the psoas muscle. Persistent thickening of the contralateral renal pelvis due to a right ureteral hematoma occurring six months earlier is also present. Trauma with baton twirling was suspected in both episodes.

ureteral bleed [17,20], and the renal pelvis may be enlarged due to obstruction by iliopsoas bleeding.

Unenhanced CT readily reveals such hemorrhages, which can be missed using contrast-enhanced CT examination alone [21]. Unenhanced CT shows renal pelvic and ureteral wall thickening, with a high-attenuation collection dissecting the layers of the ureteral wall (Fig. 3). Contrast-enhanced CT can be helpful in some instances, as it better delineates the ureter and the retroperitoneal contents (Fig. 4). CT also allows assessment of hydronephrosis and potential kidney obstruction [21]. While these findings generally disappear in 2—6 weeks [18], thickening of the renal pelvis may persist for several months (Fig. 3).

The main differential diagnosis of ureteral hemorrhage is iliopsoas or retroperitoneal hematoma. Differential diagnosis in children also includes Henoch-Schönlein purpura also called IgA vasculitis or purpura rheumatic which can cause abdominal pain and can sometimes affect the kidney leading to hematuria [22].

Scrotal hemorrhage

All scrotal abnormalities (e.g., pain, swelling, hyperemia, and bruising) require immediate evaluation, regardless of age or context. The diagnosis of scrotal hemorrhage should always be considered in hemophiliac children. In a child with scrotal hemorrhage, scrotal ultrasound shows a normal testis and a mass lining the outer margin or tunica vaginalis, with poorly-defined margins and no vascularization on color Doppler ultrasound (Fig. 5). Rarely, hematoma can also develop around the spermatic cord, showing inhomogeneous, disorganized areas along the cord's path (Fig. 6) [23]. In such cases, patients are more likely to present with inguinal pain.

Differentiating scrotal hemorrhage from testicular torsion is difficult. While torsion can occur at any age, it is more common in young and adolescent boys, with a median age of nine years [24,25]. Spermatic and testicular

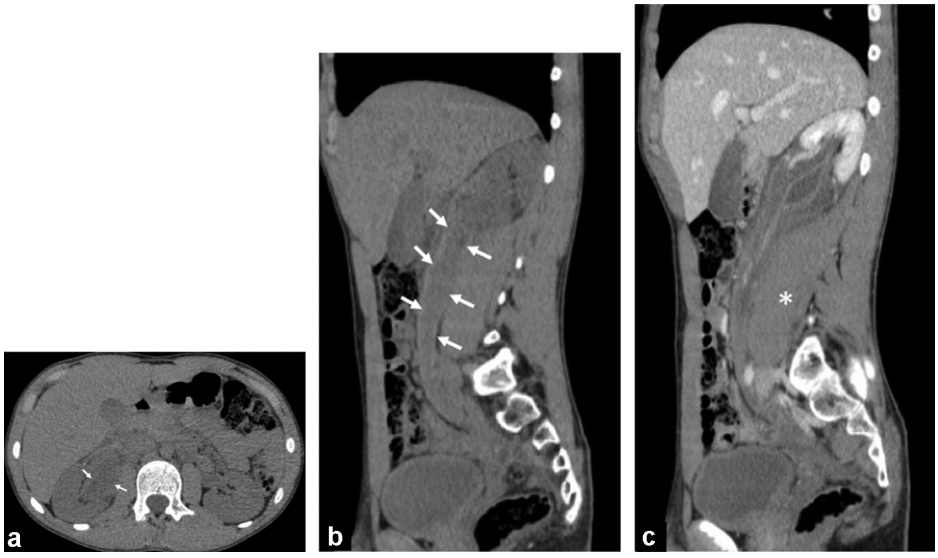

Figure 4. 17-year-old boy with severe hemophilia A. Unenhanced abdominal CT image in the transverse (A) and sagittal plane (B) and contrast-enhanced CT in the same sagittal plane (C) show a right ureteral hematoma (arrows) extending from the renal pelvis to the bladder, in front of the psoas muscle (asterisk), better demarcated after contrast injection.

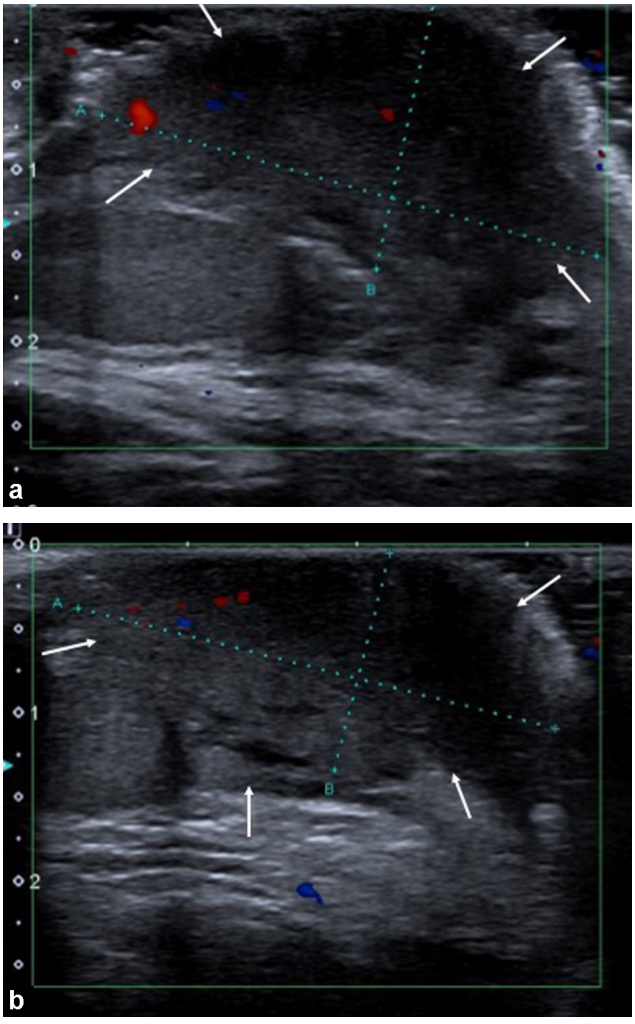

Figure 5. 4-year-old boy with severe hemophilia A presenting with acute scrotal pain and swelling of the scrotum with no reported trauma. Color Doppler ultrasound of right testis (A) and left testis (B) reveals bilateral intrascrotal hematomas (arrows) surrounding the testes, ruling out testicular torsion. Symptoms resolved within 24 hours after clotting factor replacement therapy, and surgery was avoided.

examinations with Doppler ultrasound using the appropriate gain and velocity must be used. The most reliable sign of testicular torsion is the spiral twist of the spermatic cord [26]. Other possible signs of torsion include inhomogeneous echostructure, enlarged testis and absent or reduced blood flow compared to the normal side. If there is any doubt, surgery is needed.

Outside the hemophilia context, scrotal hematoma has been described in neonates, and several potential causes have been identified, including maternal gestational diabetes, high birth weight, and birth trauma; they can also be idiopathic [27—30].

Mural and perimural hematomas of the gastrointestinal tract

Gastrointestinal hemorrhage is a well-known complication of hemophilia, with an incidence as high as 25% [31,32]. It includes mucosal bleeding, due mainly to gastric or duodenal peptic ulcers, esophagitis, and gastritis [31]. Death occurs in up to 4% of this population. In contrast, mural and perimural hematomas are very rare [33,34]. The two most common sites for spontaneous intramural gastrointestinal hematomas are the duodenum and jejunum. Patients typically present with sudden-onset abdominal pain, nausea, and vomiting due to intestinal obstruction after a large meal (Fig. 7). Patients may also present with signs of peritoneal irritation when hematoma has ruptured (Fig. 8).

Plain abdominal radiographs are no longer recommended for the diagnosis of hematoma of the gastrointestinal tract. Ultrasound demonstrates abnormal bowel wall thickening, which appears as a round, aperistaltic, tubular mass in the area of tenderness. Ultrasound may also show dilated small-bowel loops due to obstruction. Unenhanced CT is essential for diagnosis and for ruling out a surgical indication. CT shows a circumferential, hyperattenuating thickening of the bowel wall and signs of obstruction (Fig. 7) [35]. CT may also reveal an intraperitoneal rupture of the hematoma (Fig. 8). In case of doubt, MRI can show more specific imaging patterns, such as the very low signal intensity of deoxyhemoglobin on T2-weighted images, visible after 24—48 hours (Fig. 8) [34,36].

The primary differential diagnosis in child less than 3-year-old is intussusception, but it rarely affects the duodenum and jejunum. Other differential diagnoses include vasculitis such as Henoch-Schönlein purpura, inflammation or lymphoma-related bowel wall thickening. In children younger than 5-year-old, duodenal hematoma is exceptional and is mostly due to abuse related trauma.

Ultrasound is the first line imaging for any acute abdominal pain in children. However, ultrasound has limited sensitivity and specificity, while unenhanced CT can easily reveal hyperattenuating hematoma and help differentiate bleeding from another cause of thickening of the gastrointestinal wall. Mural hematoma can also be the lead point of a true intussusception [37]. At present, low-dose CT can significantly reduce ionizing radiation in children, according to the ALADA principle [38].

Pseudotumour

Hemophilic pseudotumour occurs in 1—2% of patients with severe forms of hemophilia [39,40]. It can also occur in those with moderate and mild factor deficiencies. Pseudotumours are slow-growing lesions consisting of a chronic hematoma contained within a fibrous capsule that prevents resorption and promotes neovascularization and

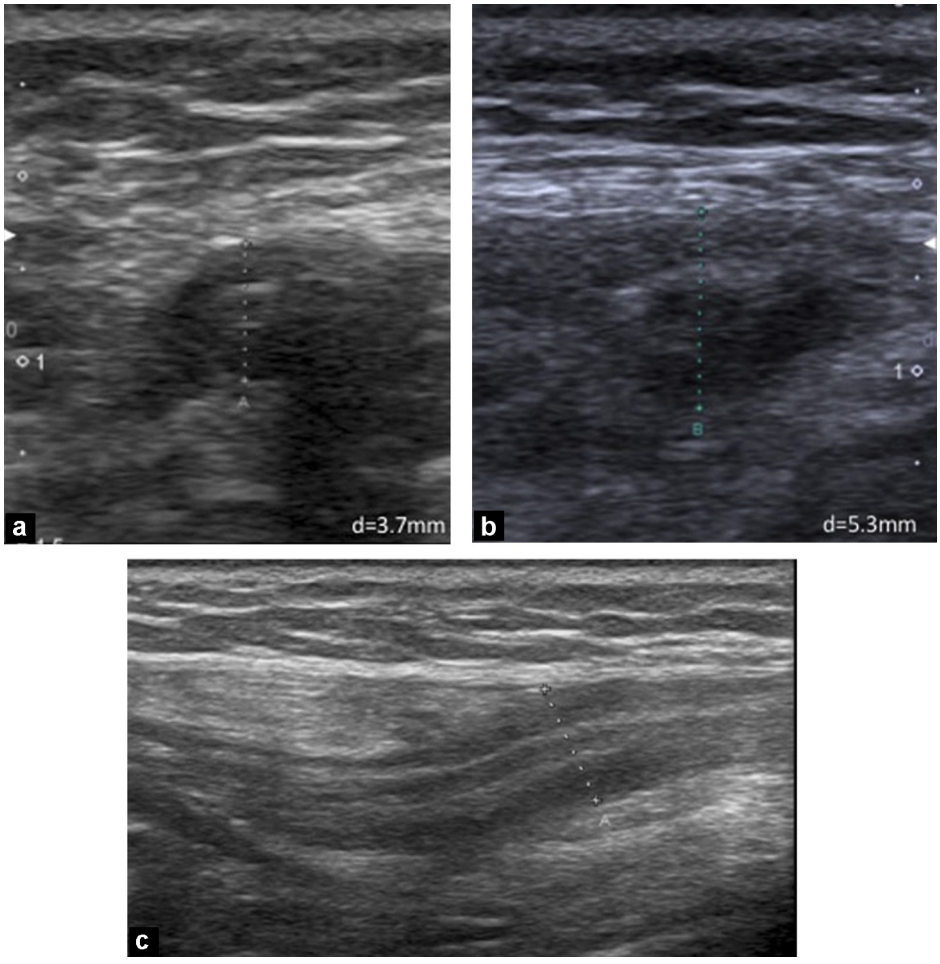

Figure 6. 4-year-old boy with severe hemophilia A presenting with left inguinal pain without trauma. Ultrasound images in the transverse plane of the right (A) and left (B) spermatic cord show a thickening of the left spermatic cord. Ultrasound image of the left spermatic cord in the sagittal plane (C) shows linear thickening of left spermatic cord, corresponding to spermatic cord hematoma. Ultrasound ruled out testicular torsion and surgery was avoided. Symptoms resolved within 24 hours after clotting factor replacement therapy.

recurrent intracapsular bleeding [40,41]. While pseudotumors themselves are generally painless, they can compress neural or vascular structures, causing symptoms [40]. There is usually a history of at least minor trauma [39]. They can be soft-tissue or osseous pseudotumors (intraosseous or sub-periosteal) [42]. Rare locations include the lungs [43], abdomen and retroperitoneal spaces [44,45], skull [46], and ileum [47]. Intrasinus hemorrhage is very rare in hemophilia; when it does occur, the maxillary sinus is the most common location [48]. Clinical symptoms include cheek swelling, nasal obstruction, rhinorrhea, intermittent facial pain, and epistaxis. Ocular asymmetry may also be noted (Fig. 9) [49]. Patients can be asymptomatic and the disease is discovered incidentally on imaging [50].

Pseudotumor is diagnosed based on clinical and imaging findings. A soft tissue pseudotumor may contain calcifications or ossifications. Adjacent bony structures may be normal or show involvement ranging from periosteal reaction to severe bone destruction with a well-defined multilobulated, expansile osteolytic lesion and cortical thinning with peripheral sclerosis. An internal fluid-fluid level may also be present. Intraosseous and sub-periosteal pseudotumor also leads to endosteal scalloping, cortical thinning and erosion and may extend into the soft-tissue [42]. CT is highly sensitive for visualizing cortical thinning, which should be smooth, with non-aggressive cortical scalloping (Fig. 9) [48,51]. If there is cortical breakthrough, however, it can mimic a tumor of the bone.

MRI is better than CT for analyzing the margins of hemophilic pseudotumours, which should be regular [44]. MRI shows several areas with different signal intensities within the mass due to blood products at various stages of aging and clot formation [38,42,52]. Regarding intrasinus pseudotumour, an intact sinus mucosa around the lesion, which is well-demonstrated on T2-weighted images, indicates a benign process (Fig. 9) [51]. The fibrous capsule appears as a hypointense, peripheral rim on T2-weighted images [42]. Contrast-enhanced CT and MRI may show marked irregular nodular, papillary, or frond-like enhancement [51,53].

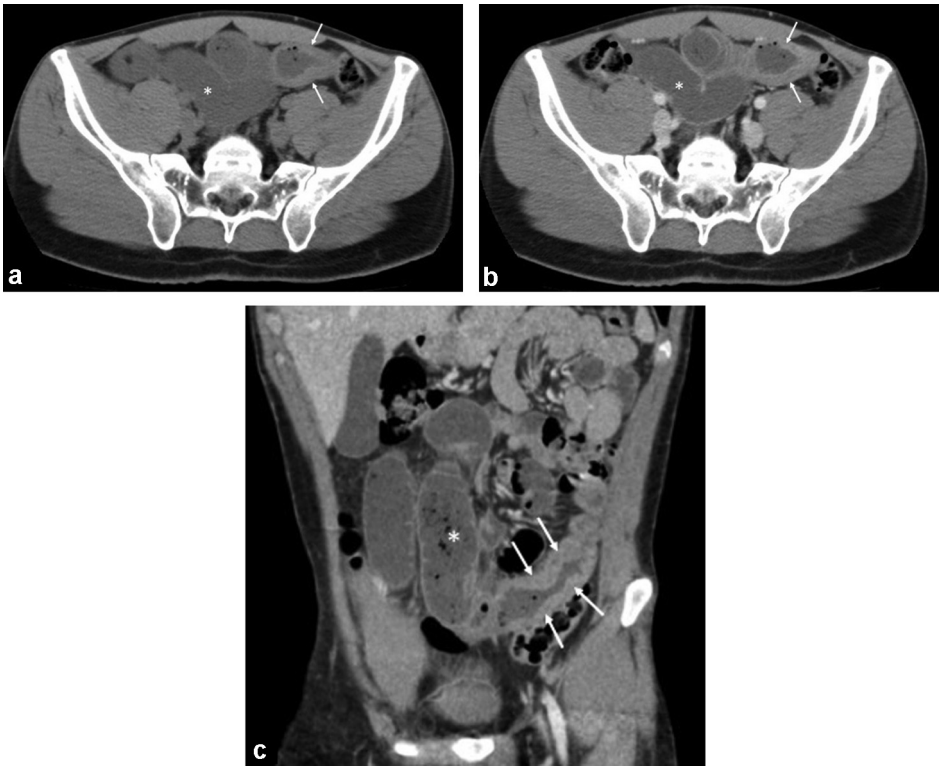

Figure 7. 26-year-old man with severe hemophilia B presenting with acute intestinal obstruction after a large meal. Unenhanced abdominal CT (A) and contrast-enhanced abdominal CT images in the transverse (B) and coronal (C) plane show hyperattenuating circumferential thickening of the small bowel wall due to intramural hematoma (arrows) and dilated bowel (asterisks) due to mechanical obstruction. This patient had repeat similar episode two years later.

In patients with severe hemophilia, the presence of typical imaging features confirms the diagnosis of pseudotumor [39]. Hematoma should always be considered in the differential diagnosis of an intrasinus mass or of an expansive soft-tissue and osseous lesion in hemophilia patients. Invasive diagnostic tests are not recommended, as they can lead to serious complications (bleeding, fistula formation, or infection). Osseous pseudotumors can mimic Ewing's sarcoma, metastasis or infection [40,42]. If there is any doubt, biopsy should be discussed, with special protocols for hemophilia patients. Surgical resection is considered only for symptomatic pseudotumors, and microinvasive endoscopic surgical approaches are preferred.

Other rare locations of hemorrhage

Intra-abdominal major organ bleeds can occur and similar to intracranial hemorrhage may reveal hemophilia in a newborn. Abdominal tenderness and distension, pallor and anemia with possible hemorrhagic shock in an hemophilic newborn suggest splenic rupture, liver or adrenal hemorrhage even without an obvious source of trauma [54—58]. Adrenal hematoma is rarely be associated with a scrotal hematoma [29]. Splenic rupture must be considered even in older hemophilic patients with abdominal pain and history of minor trauma [59]. There is usually a delayed onset of symptoms between the trauma and the splenic rupture,

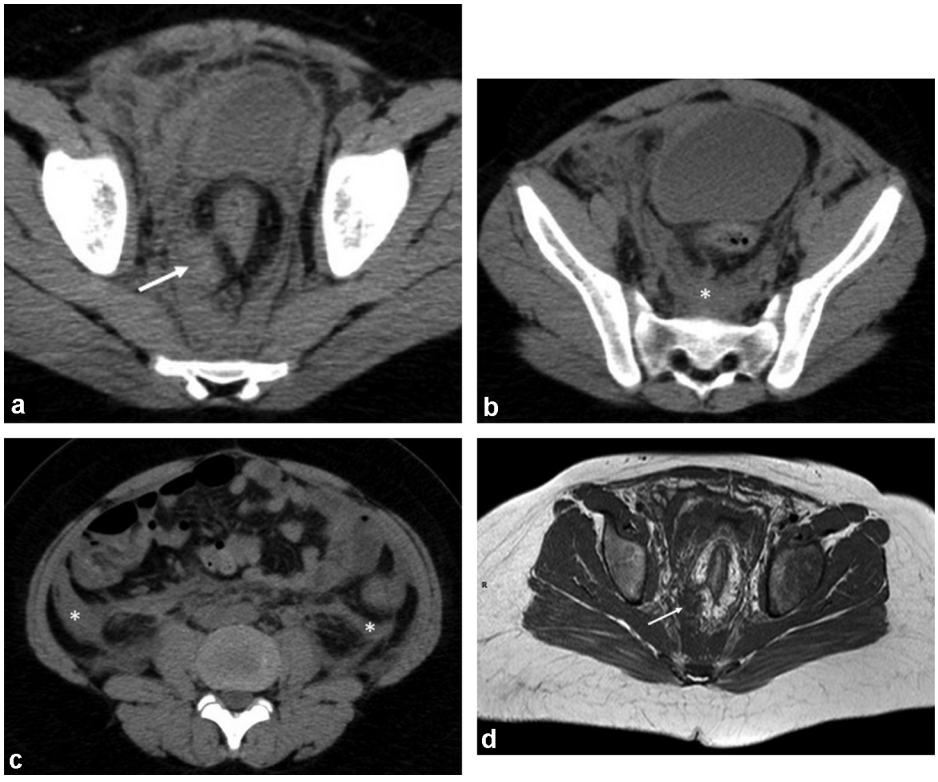

Figure 8. 10-year-old boy with severe hemophilia A presenting with acute abdominal pain, pelvic tenderness and serum hemoglobin level of 6 g/dL 24 hours after rectal lavage for longstanding constipation. Unenhanced abdominal CT images (A—C) in the transverse plane at three different levels show rectal wall hematoma that ruptured into the mesorectum (arrow) and retroperitoneal and peritoneal spaces (asterisks). T2-weighted MR image of the rectum (D) in the transverse plane shows hypointense collection in the mesorectum (arrow). The very low signal intensity strongly suggests hematoma containing deoxyhemoglobin. Rectal endoscopy confirmed a 1-cm long submucosal rectal hematoma.

suggesting the progression of a subscapular hematoma causing the rupture of the capsule [57,59]. Ultrasound examination is of great value in establishing these diagnoses.

Differential diagnosis of hemorrhagic shock in a newborn include disseminated intravascular coagulation and more rarely intraosseous bleedings [60]. Osseous bleeding in hemophiliacs can evolve towards pseudotumors. Exceptionally, hemophilia may involve girls, who are more prone to develop a hemoperitoneum with hemorrhagic shock during the ovarian follicle rupture [61].

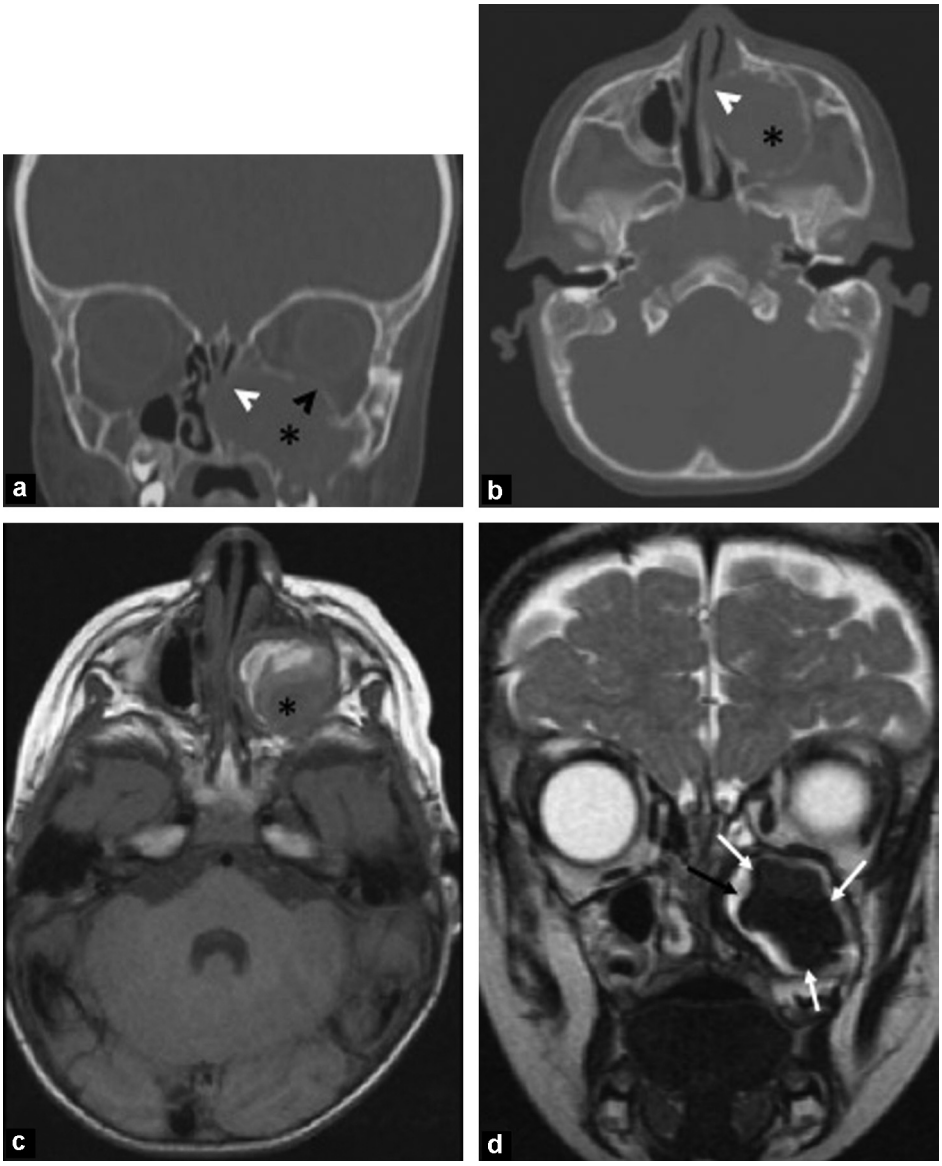

Figure 9. 15-month-old boy with moderate hemophilia B presenting with mild left exophthalmos and forehead bruising after two minor head traumas one month before. Results of neurological examination were normal. Head CT image in the coronal (A) and transverse (B) planes using bone window show a mass extending into the left maxillary sinus (asterisk), displacing the orbital floor (black arrowhead) and the medial wall of the maxillary sinus (white arrowheads) with non-aggressive cortical scalloping of the sinus walls. T1-weighted MR image in the transverse plane (C) and T2-weighted image in the coronal plane (D) reveal organized hematoma in the left maxillary sinus that appears as a well-demarcated, heterogeneous mass (asterisk) with different signal intensities and a capsule (white arrows). The intact mucosa around the lesion (black arrow) indicates a benign process. CT performed four months and eight months after long-term prophylaxis showed a shrinking of the mass, which completely disappeared four years later (not shown).

Conclusion

Pediatric and young adult hemophilia patients can present with rare, deep bleeds that make accurate clinical diagnosis a challenge. Without any delay for factor replacement therapy which is urgent in this context, imaging is invaluable to adapt appropriate close follow-up or additional treatment. The knowledge of such rare complications is important to avoid unnecessary invasive diagnostic procedures.

Disclosure of interest

The authors declare that they have no competing interest.

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