## Case Report

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# Chronic retroperitoneal hematoma with femoral neuropathy in a case of factor-II deficiency: an interesting case report

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#### **ABSTRACT**

Chronic expanding hematoma is a rare condition that develops following surgery, trauma, or injury. It can occur in the retroperitoneal region after minor trauma, potentially leading to femoral neuropathy. In this case report, we present a 22-year-old male who experienced a trivial trauma during childhood, resulting in a right retroperitoneal swelling. Clinical examination revealed a swelling measuring 18×16 cm over the right lumbar and right iliac regions, which was mobile and non-tender. Central nervous system examination showed muscle atrophy in the right thigh, an absent right knee reflex, and a complete loss of sensation in the left thigh in the L2, L3, and L4 dermatomes, corresponding to femoral and obturator nerve territories. Given the patient's history of recurrent epistaxis during childhood, coagulopathy was suspected. Investigations revealed an altered coagulation profile, and the patient was diagnosed with factor II deficiency. Contrast-enhanced computed tomography (CECT) of the abdomen and pelvis and magnetic resonance imaging (MRI) with pelvic contrast suggested differential diagnoses of chronic hematoma and soft tissue sarcoma. The diagnosis was confirmed through ultrasound (US)-guided fine-needle aspiration cytology (FNAC) of the lesion. The patient underwent retroperitoneal hematoma evacuation under general anesthesia. Intraoperative findings revealed a cavity measuring 15×10 cm in the extraperitoneal plane, bordered laterally by the iliac wing, medially by a thickened peritoneal sheath, extending inferiorly to the true pelvic brim, and superiorly to the lower border of the right kidney. Postoperative recurrent bleeding was managed with fresh frozen plasma (FFP) transfusions based on a calculated formula and daily on-demand therapy. Radiological imaging confirmed complete resolution of the hematoma postoperatively. We conclude that early surgical evacuation of chronic hematomas is critical to prevent complications such as femoral neuropathy. In this patient, delayed intervention resulted in persistent femoral nerve weakness and loss of power in the affected nerve territory.

Keywords: Chronic hematoma, Retroperitoneal mass, Coagulopathy

#### INTRODUCTION

Hematomas can develop in many locations of the body as a result of trauma, surgery, or bleeding disorders. The diagnosis of this condition is based on medical history, physical findings, and the results of examinations involving various imaging modalities. Some hematomas persist as slowly expanding, space-occupying masses for months or years, and are termed as chronic expanding hematomas (CEH).<sup>1</sup> Although hematomas caused by

surgery or trauma usually resolve without sequelae, a few persist and can undergo organization into slow-growing lesions, can be difficult to differentiate from soft tissue neoplasms.<sup>2</sup> Angiogenic tumors, in the form of angiosarcomas or benign hemangiomas, occasionally have a blood-filled appearance clinically or macroscopically. In contrast, the non-angiogenic sarcomas seldom have a blood-filled appearance. These tumor types are not generally known to form huge hematomas in the lesion. These sarcomas tend to be misdiagnosed as chronic

hematomas due to trauma. Some sarcomas, including synovial sarcoma, malignant fibrous histiocytoma and epithelioid sarcoma were described in past case reports in the literature as forming huge hematomas.<sup>3-6</sup> The magnetic resonance (MR) imaging characteristics and computed tomography (CT) findings that differentiate soft tissue sarcoma with hematoma in the lesion from chronic hematoma. Femoral neuropathy due to retroperitoneal hematoma has been infrequently described in the literature. The location of the pelvic portion of the femoral nerve between the iliacus and psoas muscles makes the nerve particularly vulnerable in hemorrhage within the iliacus. The iliacus hematoma syndrome consists of a compression neuropathy of the femoral nerve subsequent to hemorrhage within the iliacus. Patients with iliacus hematoma syndrome characteristically exhibit a large, painful, tender, globular swelling due to hemorrhage in the iliac fossa. Goodfellow et al reported three cases where an additional fusiform mass developed in the psoas fascial compartment, with a palpable groove between the distended psoas and iliacus muscles.7 There may sometimes be swelling in the groin, severe pain and sensory loss along the distribution of the femoral nerve, and weakness or paralysis of the quadriceps muscle are frequently encountered.<sup>8</sup> Sometimes the pain radiates into the lumbar area, occasionally producing a secondary scoliosis. A puzzling phenomenon, however, is the position of the hip, which is characteristically flexed, abducted, and externally rotated. This peculiar hip position affords maximum relief from severe pain by reducing tension on the femoral nerve, which is stretched over the bulging hematoma.<sup>9</sup> The management of retroperitoneal hematoma with consequent femoral nerve palsy remains controversial. Hematoma evacuation at the time of the development of femoral neuropathy results in immediate benefit, with greater likelihood of a return to pre-event neurological status. Delays in operative treatment, despite the presence of a neurological deficit, may lead to significant and prolonged neurological dysfunction. Surgical decompression should be highly considered in all patients who develop femoral neuropathy from a retroperitoneal hematoma.

#### **CASE REPORT**

A case of 22-year-old male patient with prior history of trivial trauma in July 2019 followed by which he was admitted in nearby medical college with swelling over right abdomen and leg associated with fever was evaluated with venous Doppler of right lower limb to rule out deep vein thrombosis, intravenous pyelogram suggestive of Right hydronephrosis. With differential diagnosis of psoas abscess and retroperitoneal hematoma patient underwent contrast enhanced computed tomography (CECT) abdomen with pelvis which suggestive of retroperitoneal hematoma and diagnosed as right lower limb cellulitis with right retroperitoneal hematoma with suspicious of coagulpathy disorder due to altered PT-INR values and history of frequent epistaxsis in childhood for which computed tomography (CT) -angiogram done suggestive

possibility of abnormal lilac-arteriovenous malformation. He came to JIPMER Hospital for further management in 2019 to CTVS department planned for digital subtraction angiography (DSA) followed by radio coil embolization of feeding vessels but patient lost follow up for 2 years. Now he presented to our JIPMER outpatient department (OPD) of general surgery on November 2021 with previous mentioned swelling over right flank region was increasing in size and associated with pain radiating to right thigh which was dull aching, continuous, low grade aggravated on walking and lying supine, relieved on lying down on side with flexed right lower limb for past 2 months associated with numbness in right thigh and bucking of the right knee leading to difficulty in walking for past 1 month. On examination conscious, oriented. pallor present. Per abdomen showed swelling of size 18×16 cm over the right lumbar and right lilac region which was mobile, non-tender. Central nervous system examination showed loss of muscle bulk in right thigh region, and right knee reflex absent, all sensation lost in left thigh in L2, L3, L4 dermatomes - femoral and obituary or nerve territory, power of lower limb (Table 1). Since coagulopathy was suspected patient referred to medicine department where he got admitted with provisional diagnosis of an inherited coagulation disorder, coagulation profile showed prolonged prothrombin time (PT) - 27.7 and international normalized ratio (INR) - 2 with activated partial thromboplastin time (aPTT) - 59.8 and normal thrombin time (TT) - 15.4. Based on common pathway defect was suspected and factor specific testing was done for factors II, V, X. Factor II activity was found to be 4% and the patient was diagnosed as factor II deficiency (FIID) and referred back to surgery. Further evaluation done with CECT abdomen and pelvis suggestive of welldefined heterogeneous soft tissue dense lesion showing multiple hyperdense areas and fluid-fluid level suggestive of hemorrhage within in the right lumbar region extending to pelvis. No significant enhancement seen possibility of hematoma, bony erosions, irregularity with ill-defined lytic areas in right lilac wing (Figures 1a and b). Magnetic resonance imaging (MRI) with pelvic contrast suggestive of large well defined heterogeneous T1/T2 variable signal intensity retroperitoneal mass in the right lumbar region and right lilac fossa involving the right Iliacus muscle, psoas muscle extending into right sacroiliac joint pat and posteriorly involving gluteus muscles through smooth bony defects in the right lilac bone possibility of soft tissue sarcoma (Figures 2 a-d). Patient was planned for hematoma evacuation after CECT abdomen but deferred in view of MRI suggested of soft tissue sarcoma arising from right lilac bone. So, decision made to proceed with ultrasound (US) guided fine needle aspiration cytology (FNAC) from lesion, after transfusing fresh frozen plasma (FFP) and normalizing PT-INR. FNAC done revealed possibility of chronic hematoma can be considered with no visible malignant cells in multiple section. Now planned to proceed with previous plan and patient underwent retroperitoneal hematoma evacuation under general anesthesia, intraoperative findings are cavity of size  $15 \times 10$ cm noted in the extra peritoneal plane bordered by lilac wing laterally, thickened peritoneal sheath medially, lower extent reaching up to true pelvic brim, upper reaching till lower border of right kidney. Cavity contained mixed components of recent hematoma, chronic hematoma, hemosiderin debris, necrotic muscle tissue with no any well-defined capsule. So, complete evacuation of the contents done, fresh ooze noted from the iliac wing periosteal surface. Saline wash given and hemostatis achieved by hemostatic agents. Wound left open and applied compression dressing.

On postoperative day (POD) -4 secondary suturing of wound done. On POD-8, there was sudden increase in swelling around the surgical site with tachycardia and hypotension, he was immediately taken to operative room and underwent retroperitoneal exploration with operative findings of 200 ml clotted blood, active ooze from the periosteal surface of lilac blade stopped by using fibrin sealant injection, wound closed in layers with drain kept in the cavity (Figure 3).

Postoperatively transfusion medicine opinion obtained and was advised to repeat factor II activity and was started on fresh frozen plasma, serial PT, aPTT, and INR done (Table 2). Factor II activity repeated was 4.9%.

Table 1: Power of lower extremity muscle group.

Power and movements	Right	Left
Hip		
Flexion	4/5	5/5
Extension	5/5	5/5
Abduction	5/5	5/5
Adduction	3/5	5/5
Knee		
Flexion	4/5	5/5
Extension	2/5	5/5
Ankle		
Dorsi-flexion	5/5	5/5
Plantar flexion	5/5	5/5

Table 2: Serial PT-INR respective to postoperative days.

Post-operative day (POD)	Prothrombin time	PT- INR	aPTT
POD-4	18.3	1.57	35.1
POD-9	17.7	1.52	36.8
POD-10	15.3	1.31	23.1
POD-11	12.3	1.04	31
POD-13	13.9	1.17	35.4
POD-14	13.5	1.14	37.6
POD-15	11.8	1.21	32.8
POD-17	15.1	1.27	38.5
POD-22	14.6	1.23	37.5

Total FFP's to be given is calculated by the following formula.

#### Formula for total blood volume (TBV)

 $TBV = Total\ body\ weight\ (kg)$   $\times\ average\ blood\ volume\ (ml/kg)$ 

Here, weight of patient is 58 kg, and for males, average blood volume is 75 ml/kg.

$$TBV = 58 \times 75 = 4350 \ ml$$

#### Formula for total plasma volume (TPV)

 $TPV = TBV \times (1-Hematocrit)$ 

Here, hematocrit (HCT) is 0.35 (35%).

$$TPV = 4350 \times (1-0.35) = 4350 \times 0.65 = 2827.5 \, ml$$

#### Formula for total FFP's required

Total FFP's required

= [(Desired factor

- II value-current factor

 $-II \ value) \div 100$ 

× plasma volume

Here, desired factor-II value is 50%, current factor-II value is 5%, and plasma volume is 2827.5 ml.

Total FFP's required = 
$$[(50-5) \div 100] \times 2827.5$$
  
=  $0.45 \times 2827.5 = 1272.375 IU$ 

# Formula for fresh frozen plasma (FFP) units required per day

*FFP* units required per day

= Total FFP's required

÷ volume of FFP's in 1 unit

Here, volume of FFP's in 1 unit is 150 IU.

FFP units required per day = 
$$1272.375 \div 150$$
  
  $\approx 8$  FFP units

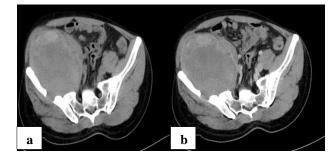


Figure 1: (a) Plain and b) post contrast CT images show a large hyperdense minimally enhancing lesion with few fluid-fluid levels within centered in the right iliopsoas muscle causing erosions of the right iliac bone.

So total 8 FFP's was given daily to attain the desired 50% factor II level and drain output monitored serially. After 10 days of FFP transfusion on POD-18 from initial surgery, repeat factor 2 assay sent is 51.7% and the nature of drain fluid turned sero-sanginous from sanginous. Repeat CECT abdomen on POD-18 suggestive of small retroperitoneal collection of size 5×5 cm possibly hematoma and drain tube noted within the collection (Figure 4).

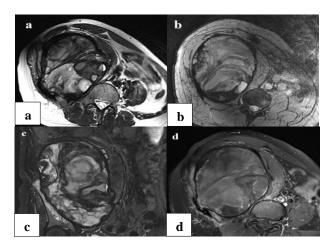


Figure 2: Shows a) axial T2 weighted MRI image shows a heterogeneous predominantly hypointense lesion with fluid-fluid level within centered in the right iliopsoas muscle causing erosions in the right iliac bone; b) axial medic sequence shows peripheral blooming, raising the suspicion for a hematoma; c) coronal TIRM sequence shows a heterogeneous predominantly hypointense lesion with few hyperintense areas within, underlying right iliac bone shows signal abnormalities; and d) axial T1 weighted post contrast image shows minimal peripheral enhancement and enhancement of the internal septae.

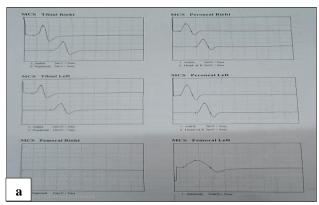


Figure 3: Postoperative suture with drain in-situ.

Transfusion medicine opinion was sought, advised to decrease FFP transfusions to 6 units per day to attain 40% factor II level as drain output is in decreasing trend, after 5 days on POD-23 repeat factor 2 assay sent is 41.2%, next day all sutures were removed and discharged with drain in situ. Advised for follow up in OPD basis with daily drain output charting.



Figure 4: Immediate post-operative CT scan shows bulky right psoas muscle with collection and internal air foci. Drain tube is seen within.



Site	Latency (ms)	Amplitude (mV)	Area (mVms	Segment	Distance (mm)	Interval (ms)	NCV (m/s)	NCV N.D
Tibial, R	•	•		•		•	•	
Ankle	3.6	11.19	28.06	Ankle		3.60		
Popliteal	11.1	10.20	29.12	Ankle- popliteal	400	7.50	53.3	
Peroneal, R								
Ankle	3.15	8.82	24.74	Ankle		3.15		
Head of	9.65	8.26	23.26	Ankle- Head of Fibula	330	6.5	50.8	
Fibula Tibial, L				OI FIDUIA				
Ankle	4.1	17.55	38.33	Ankle		4.10		
Popliteal	11.8	13.60	38.83	Ankle- popliteal	400	7.70	51.9	
Peroneal, L			1	popiicai	1		1	_
Ankle	3	11.24	29.98	Ankle		3.00		
Head of Fibula	9.05	10.17	28.95	Ankle- Head of Fibula	330	6.05	54.5	
Femoral, R								
Inguinal	NR	NR	NR	Quadriceps				
Femoral, L	•	•	•	•		•		
Inguinal	3.75	14.40	95.82	Quadriceps		3.75		
F-Wa	ve Study:							

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Figure 5: (a) ENMG layout of motor nerves conduction study showing right femoral motor neuropathy; and b) motor and sensory nerves conduction study at ENMG showing a motor a right lumbosacral plexpathy.



Figure 6: Post-operative scar on 6 months follow-up.

Patient came on POD-34 for follow up with daily drain output of average less than 20 ml with serous nature and still had persistent right lower limb weakness and numbness. Advised for repeat US local area suggestive of 2×2 cm hypoechoic collection. So, drain tube removed and asked to follow up as of need. Patient came first follow up after 6 months, with no any complaints and postoperative scar was healthy (Figure 5) and repeat CECT abdomen with pelvis done shows bulky right psoas muscle and no residual hematoma (Figure 7a) and he was fine with no any right flank swelling but persist to have right lower limb weakness. The patient was advised for neurology opinion, evaluated by electroneuromyogram (ENMG) suggestive of right femoral motor neuropathy with lumbosacral plexopathy (Figures 6a and b) and MR lumbo-sacral spine and pelvis suggestive of heterogeneous hyper intense areas in right illiacus and posterior fibers of psoas muscle with altered signal intensity and cortical irregularity of right illac wing with no obvious localised collection.

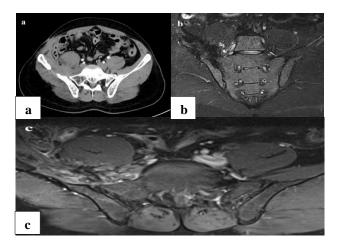


Figure 7: Shows (a) post-operative CECT scan (after 6 months) shows bulky right psoas muscle and no residual hematoma; b) coronal TRIM sequence shows hyperintense signal changes along the right lumbar plexus, no residual hematoma is seen; and (c) axial T1 weighted post contrast MRI shows smooth enhancement along the lumbar plexus. No residual hematoma is seen.

Hyper intense thickening of ventral roots of right L3-L5 nerves with mild post contrast enhancement possibility of

lumbar plexopathy secondary to previous psoas hematoma (Figures 7b and c). Repeat factor II activity done after 3 months is 6.5%. So this clearly tells that the treatment for retroperitoneal hematoma with FIID should be individualized and the purpose is to maintain factor 2 levels as enough as required level for normal hemostasis, traditional treatment for patients is on-demand therapy that means beginning of treatment as soon as possible after bleeding, but secondary prophylaxis can be considered for those with high risk of life threatening bleeding.

#### DISCUSSION

Chronic expanding hematomas (CEH) is a type of hematoma that is most commonly caused by trauma, and has certain other etiologies such as hemorrhagic disorder. Hematomas are often reabsorbed, and gradually decrease in size. However, in rare cases, they may develop slowly and expand progressively over a period of time. In certain cases, CEH may persist and increase in size for more than 1 month after the initial hemorrhagic event. Hematomas in the skeletal muscles or surrounding tissue may develop as a result of a direct shearing force that splits the subcutaneous fat from the underlying fascia, thus potentially creating a large space, which may then fill with blood. Labadie et al reported that blood and erythrocyte degradation products, hemoglobin, leukocytes, platelets, and fibrin exert an irritant effect on the surrounding tissue.10 These factors are believed to induce a mild inflammatory response, which increases vascular wall permeability and bleeding from dilated capillaries in the granulation tissue beneath the capsular wall, thus resulting in the subsequent growth of the hematoma. Generally, the most common clinical manifestations in patients with FIID are epistaxis, prolonged and heavy menstruation, bleeding in joints and muscles and bleeding from mouth and gums. Gastrointestinal bleeding, umbilical cord bleeding and bleeding after major or minor surgeries are occasionally reported in these patients, while severe life-threatening bleeding such as intracranial hemorrhage are reported in less than 10% of patients. 11,12 Like in our case patient had previous episode of spontaneous epistaxsis during his childhood which was not evaluated. PT and aPTT are usually sensitive enough to detect coagulation factors abnormalities, but their results may be normal in some coagulation factors deficiency including fibrinogen, prothrombin and FXIII. Therefore, diagnosis of FIID may require specific assessments. 13,14 The femoral nerve develops within the body of the psoas muscle from the posterior divisions of L2-L4. The femoral nerve then runs between the psoas tendon and iliacus muscle beneath the iliacus fascia to the femoral canal, under the inguinal ligament to provide motor and sensory innervation to the leg. Anatomic studies have revealed that the fascia overlying the iliacus muscle and the femoral nerve is strong and not easily stretched in the presence of underlying hematoma formation.<sup>15</sup> The femoral nerve provides motor innervation to the quadriceps, sartorius, pectins, and iliopsoas muscle and supplies sensory innervation to the anteromedial thigh and medial leg. It lies

between the iliacus and psoas muscles, which form a tendon inserting into the lesser trochanter of the femur. The entrapment of the femoral nerve in this area due to hematoma causes weakness in hip flexion and knee extension and has been reported more widely after hematologic disorders such as haemophilia. 16 The clinical presentation of a retroperitoneal hematoma is usually marked by the sudden onset of severe pain in the affected groin and hip, with radiation to the anterior thigh and the lumbar region. Iliacus muscle spasm often results in the characteristic flexion and external rotation of the hip. Any attempt to extend the hip results in severe pain. Femoral nerve involvement is noted initially by the development of pain in the anteromedial thigh and leg followed by paresthesia in the same distribution. Motor findings may follow and include quadriceps weakness and eventual paralysis.<sup>17</sup> In face of progressive neurological dysfunction, however, operative intervention should be urgently undertaken.<sup>18</sup> In our case the femoral nerve compression signs and symptoms present as a chronic feature which usually present in acute setting as per literature. Liu et al reported that CEH should be considered in the differential diagnosis for soft tissue masses that exhibit internal hemorrhage and fibrous pseudocapsule during unenhanced T1- and T2-weighted MRI. If the contrast enhancement is patchy within the lesion, a diagnosis of hemorrhagic sarcomas should be considered.<sup>19</sup> In sarcomas associated with hematomas, it is difficult to reach the correct diagnosis via aspiration biopsy cytology, because tumor cells are often not obtained from these biopsy specimens.20 Imaizumi et al series of studies performed in all six patients, aspiration biopsy cytology performed however, in five of the patients, no malignant cells were obtained.<sup>21</sup> Therefore, clinicians should always be on the alert to detect fine lesion enhancement on MRI. In chronic hematomas caused by trauma, enhancement of the peripheral wall was shown, indicating reactive growth and appearing much like a sarcomatous mass.<sup>22</sup> We believe that an open biopsy should be performed without delay in a patient with a soft tissue tumor when it is clinically and radiographically impossible to differentiate from chronic hematoma from sarcoma. The key to the correct diagnosis of chronic hematomas is the confirmation of a history of trauma. Therefore, a history of trauma should be taken into account,

As it may lead the clinician to the correct diagnosis of chronic hematoma. 23,24 The misdiagnoses of the six sarcomas as hematomas was attributable, in part, to the lack of a clear history of trauma. Meticulous evaluation of both MR imaging findings and clinical information is important for differentiating chronic hematoma from soft tissue sarcoma. 21 We conclude that intramuscular hematomas following trauma should be approached with a high degree of clinical suspicion. MRI analysis can be used as an important diagnostic tool, but the results must be seen in the context of the clinical history. MRI is not sensitive or specific enough to rule out malignancy. The diagnosis of a high-grade sarcoma must be considered in these

patients and any doubt should be resolved with a biopsy.<sup>25</sup> As in our case the ultrasound guided (US) FNAC did not reveal malignant cells but the differential diagnosis of sarcoma was not ruled out until surgery. The treatment of retroperitoneal hematoma with associated femoral neuropathy remains controversial. In the presence of inherited disorders such as hemophilia, it has generally been accepted that factor replacement and a conservative non operative approach can be taken with good functional results, if treatment is initiated early.<sup>26</sup> Patients with FIID usually require on-demand replacement therapy, but prophylaxis may be used for those patients at high risk of severe life-threatening hemorrhages. Diagnosis of disorder is made based on simultaneous prolongation of PT and aPTT and decreased FII activity. 27 The main treatment of prothrombin deficiency is replacement therapy using FFP and prothrombin complex concentrate (PCC). Moreover, administration of antifibrinolytic agents, with or without replacement therapy, can be useful in the management of mild bleeding episodes. Administration of antifibrinolytic agents accompanied by PCC is contraindicated because thrombotic complications are potential risk of PCC injection and fibrinolysis is the only body defending mechanism against undesirable clot formation.<sup>28</sup> Most of PCCs are containing therapeutic amounts of three coagulation factors: FII, FIX and FX. There are also PCCs containing four coagulation factors that have FVII in addition to above.<sup>29,30</sup> In absence of a proper PCC, viral inactivated FFP can be administered as source of prothrombin. Although viral inactivation can eliminate blood born infections, other complications of blood products injection are remain including inhibitor formation, thrombosis and rash.<sup>13</sup> Patients cardiovascular diseases are at risk for circulatory overload; so it is better to inject PCC instead of FFP in these patients.<sup>31</sup> The correct treatment for the CEH is only surgical. Aspiration of the liquid, drainage and curettage could result in serious bleeding and have a higher possibility for recurrence. Complete resection of the capsule and a meticulous suture of the subcutaneous tissue, with the underlying fascia in order to eliminate the dead space are highly recommended. 32-34 Complete removal of the hematoma with fibrous capsule is recommended. But in some cases, it is difficult to remove because of abundant new vascularization beneath the capsule and the presence of a severe adhesion to the surrounding structures. Incomplete treatment, such as drainage and curettage of the contents, would result in recurrence or massive bleeding from the hypervascular subcapsular lesion.<sup>2</sup> By using CT in particular, the presence of new capillaries and granulation tissue can be easily identified if contrast material is used.35

#### **CONCLUSION**

This case study highlights the critical role of a detailed medical history, particularly previous trauma and childhood epistaxis, in evaluating coagulation disorders and distinguishing them from sarcomas, which may present with similar radiological findings. Diagnosis in

this case was confirmed through ultrasound-guided FNAC, which ruled out malignancy. Early surgical evacuation of the hematoma is emphasized as essential to prevent complications such as femoral neuropathy. Delayed intervention, as seen in this patient, resulted in persistent femoral nerve weakness and loss of power in the nerve's territory even six-months post-surgery. Ondemand replacement therapy for factor II deficiency remains the gold standard, as confirmed by persistently low factor II levels on repeat assay after three months. Notably, the patient experienced no recurrence of symptoms following this treatment approach. This case underscores the importance of timely hematoma evacuation in patients presenting with femoral neuropathy and coagulopathy for preventing long-term neurological deficits combined with targeted on-demand therapy, as the optimal treatment strategy.

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