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Case Report

Subperiosteal hemorrhage: A rare complication in neurofibromatosis which may mimic malignant peripheral nerve sheath tumor

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ABSTRACT

Currently, there is little in the medical literature on subperiosteal hematomas in neurofibromatosis patients, particularly in those who have subperiosteal neurofibromas. Initial imaging and clinical presentation can be very worrisome and to the unaware may lead to early surgical intervention and/or anxiety in the patient and parents. This report presents the case of a 9-year-old child with neurofibromatosis type-1 and progressively increasing calf pain and swelling about a known plexiform neurofibroma. Imaging at initial presentation and at 1 month demonstrated evolving subperiosteal hemorrhage. This report adds to the small body of literature on subperiosteal hemorrhage as a complication of neurofibromatosis. Additionally, this report demonstrates an approach to noninvasive management of these lesions with the utility of initial and 1 month follow-up radiographs helpful in demonstrating hemorrhage evolution and possibly negating the need for biopsy.

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Introduction

First comprehensively described by Smith in 1849, with the true histology of the tumor elucidated by von Recklinghausen in 1882, neurofibromatosis type 1 (NF-1) is the most common phakomatosis with marked variability in clinical manifestations and a progressive clinical course [1,2]. Up to 50% of patients will have skeletal manifestations [3]. Much of the skeletal manifestations have been described in detail and are

well known to the pediatric radiologist, that is, bone dysplasia, osseous bowing, tibial pseudarthrosis, short-segment scoliosis, dural ectasia, and limb gigantism, in addition to others. Two very rare manifestations of NF-1 are subperiosteal hemorrhage and subperiosteal neurogenic tumors. This report describes a case of a subperiosteal hemorrhagic pseudotumor with interesting imaging features. The authors will then provide a brief discussion on the pathophysiology of subperiosteal hemorrhage in NF, key imaging features which help to differentiate bland hemorrhage from hemorrhage related to

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benign or malignant peripheral nerve sheath tumors (MPNST) in the subperiosteum, a proposed imaging follow-up timeline, and recommendations for when additional intervention is needed to exclude an underlying tumor, that is, when biopsy is necessary.

Case report

A 9-year-old male with known NF-1 presented to our institution with a 5-month history of increasing left calf size and pain in the region of a known plexiform neurofibroma. The patient experienced no significant trauma prior to presentation and has no personal or family history of bleeding disorders. The patient was not on any anticoagulants. Initial MRI demonstrated a large tibial subperiosteal heterogeneous mass with areas of cystic change, hemorrhage, a focal T2 targetoid lesion (central T2 hypointensity with a circumferential rim of hyperintensity), heterogeneous enhancement, and patchy adjacent edema (Fig. 1). The periosteum was uplifted, and there was an irregular area of periosteal reaction and questionable extraperiosteal extension. Previous MRI imaging demonstrated no findings of hemorrhage but did show a very subtle subperiosteal/periosteal neurofibroma (Fig. 2) at the site of the patient's hemorrhagic mass. Although the subperiosteal lesion was largely comprised of hemorrhage, due to the clinical history and the question of an internal neurogenic component, a repeat MRI was obtained at 1 month. MRI imaging at that time (Fig. 3) demonstrated decreased hemorrhagic and cystic components. There was increased patchy, predominantly peripheral enhancement. The periosteum remained uplifted with maturation of the periosteum along the anterior margin of the lesion. Concurrent radiographs (Fig. 4) demonstrated the peripheral calcification of the periosteum with no aggressive periostitis. The mass was subsequently biopsied with CT guidance along the anterior most aspect of the lesion with pathologic analyzes consistent with evolving hemorrhage. No neural elements were demonstrated on the biopsy specimen. The patient did well post biopsy. No additional specific intervention was required once the biopsy results confirmed the nature of the lesion. At 1-year follow-up, the patient had not had any evidence of recurrent subperiosteal hematoma.

Discussion

Affecting 2-3/10,000 population, neurofibromatosis is the most common phakomatosis [4]. There are rare case reports of spontaneous subperiosteal hemorrhage in NF-1 patients with 2 reports demonstrating the subperiosteal neurofibromas with concomitant hemorrhage, this case being the third [3–10].

The pathogenesis of subperiosteal hemorrhage is thought to be from 2 factors, vascular fragility and weakened periosteal attachment secondary to mesodermal dysplasia and/or periosteal involvement by a plexiform neurofibroma [8]. With little or no trauma, large and recurrent subperiosteal hemorrhages can occur [3]. At the same time, the periosteal and

subperiosteal spaces can be involved with neurofibromas thought to arise from periosteal nerves [5,8]. When small, these can be occult on imaging. However, once enlarged and if benign, subperiosteal neurofibromas/plexiform neurofibromas generally demonstrate the typical targetoid appearance on MRI with central T2 hypointensity and peripheral T2 hyperintensity [11].

Notably, NF-1 patients have a 2%-5% lifetime risk of malignant degeneration in a pre-existing plexiform neurofibroma [11]. Thus, on initial evaluation, and to the unwary radiologist, subperiosteal hemorrhages may raise the concern for malignant degeneration. At the same time, it is important for those who are familiar with the association of NF and subperiosteal hemorrhage to be aware of and look for possible periosteal and subperiosteal plexiform neurofibromas. However, to the best of our knowledge, there has not been a reported case of a subperiosteal malignant peripheral nerve sheath tumor with simultaneous subperiosteal hemorrhage.

Levell et al. provided a very detailed history of the findings of subperiosteal hematoma with a review of literature to date on reported cases [8]. The authors also propose an evolution of imaging findings in patients with NF and subperiosteal hematoma. Our case demonstrates similar features. What is difficult to distinguish and what has not been reported in the literature is systematic evaluation and follow-up.

First, the initial imaging should be deeply scrutinized. Many patients with neurofibromatosis have previous imaging. These comparison studies should be evaluated for subtle subperiosteal or periosteal neurofibromas. In this case, the neurofibroma within the tibial subperiosteum is nearly imperceptible. Next, the current imaging features should be reviewed. Classically, acute hemorrhagic products are hyperintense on T1WI. The subperiosteal location can be confirmed by noting the lenticular or fusiform-shaped lesion morphology. As the blood products age, the hematoma loses its T1 hyperintensity and becomes T2 hyperintense. Further signal progression to T1 and T2 hyperintensity develops until, ultimately, the hematoma becomes hypointense on both. The periosteum is demonstrated as a peripheral hypointense curvilinear structure confining the hematoma. Thickening and irregularity of the periosteum may be seen and is not a definitive finding of malignancy. Rather, this reflects the progressive peripheral ossification that may develop in some hematomas. In older literature, this ossifying stage has been referred to, somewhat confusingly, as a subperiosteal bone cyst [6]. Interestingly, in the cases where these subperiosteal bone cysts were surgically removed, neurofibroma elements were seen at pathology, suggesting that more than mesenchymal dysplasia and loose periosteal connections may be at play.

Differentiating a malignant peripheral nerve sheath tumor from bland subperiosteal hemorrhage is quite difficult. In a study by Wasa et al., the authors demonstrated a 90% specificity for malignant peripheral nerve sheath tumors who presented with 2 or more findings of heterogeneous T1 signal, perilesional edema, peripheral enhancement, and cystic change [12]. As this case demonstrates, these exact findings may also be present in bland subperiosteal hematoma. Furthermore, increased swelling and pain in the region of a known neurofibroma are clinical hallmarks of malignant degeneration. However, these too can be present in subperiosteal

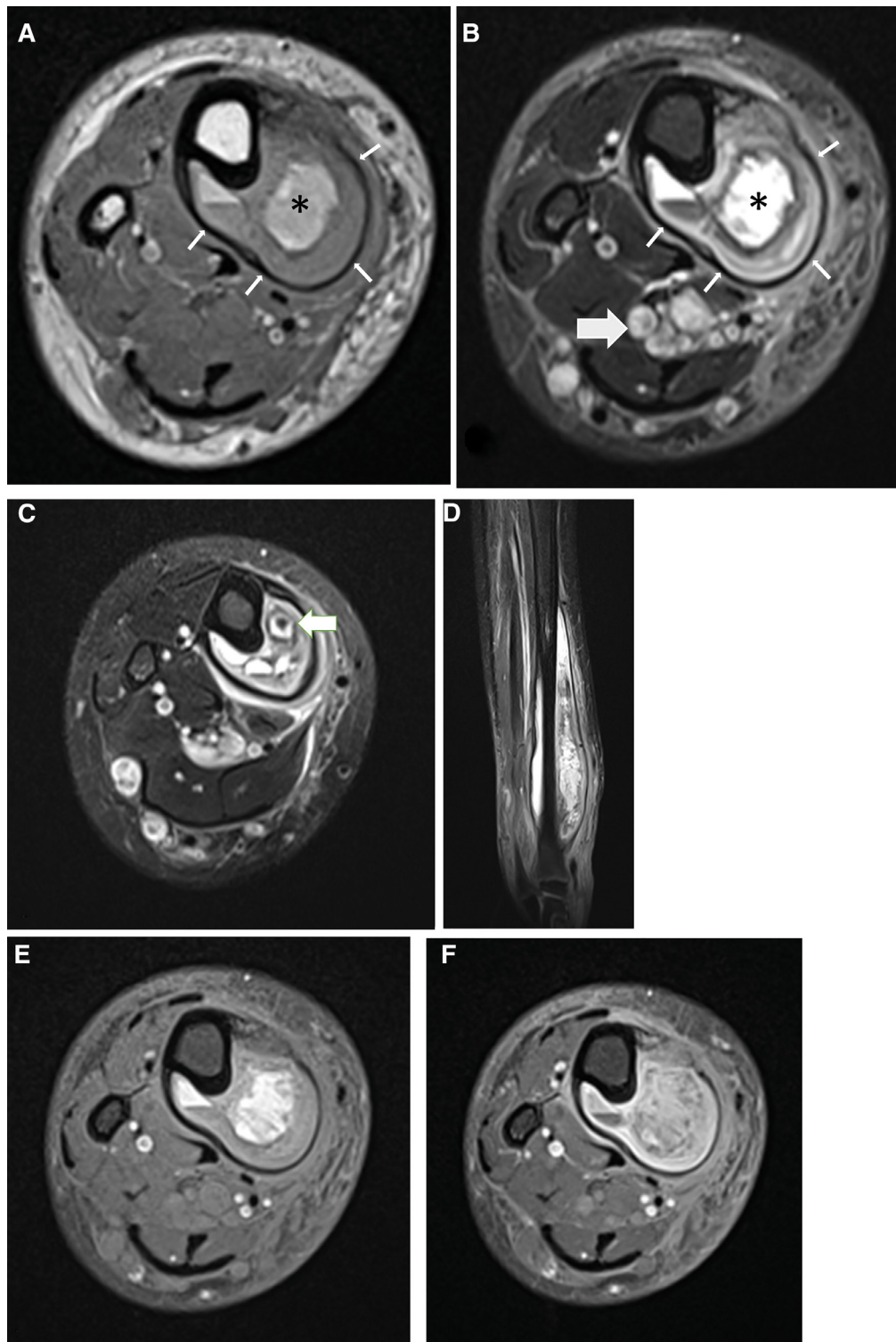


Fig. 1 – A 9-year-old male with neurofibromatosis type 1, a subperiosteal hematoma, and neurofibromas. (A/B) Axial T1- and T2-weighted MR images of the leg demonstrated a heterogeneous, subperiosteal lesion with focal areas of T1 hyperintensity (*) representing blood products and internal cystic foci. The periosteum is uplifted (thin arrows in A/B) and irregular anteriorly. Soft tissue edema surrounds the lesion. Several neurofibromas with a posterior plexiform neurofibroma (larger arrow in B) can be seen in the adjacent soft tissues. (C) Axial T2-weighted images inferior to A and B demonstrate the classic targetoid appearance of a neurofibroma with internal hypointensity and ring of T2 hyperintensity (arrow). Additional cystic foci within the lesion are also well depicted. (D) Sagittal STIR image shows the full extent of the lesion. (E/F) Pre (E) and postcontrast material-enhanced (F) T1-weighted images with fat-saturation demonstrate corresponding peripheral enhancement about the lesion as well as within the area of irregular periostitis.

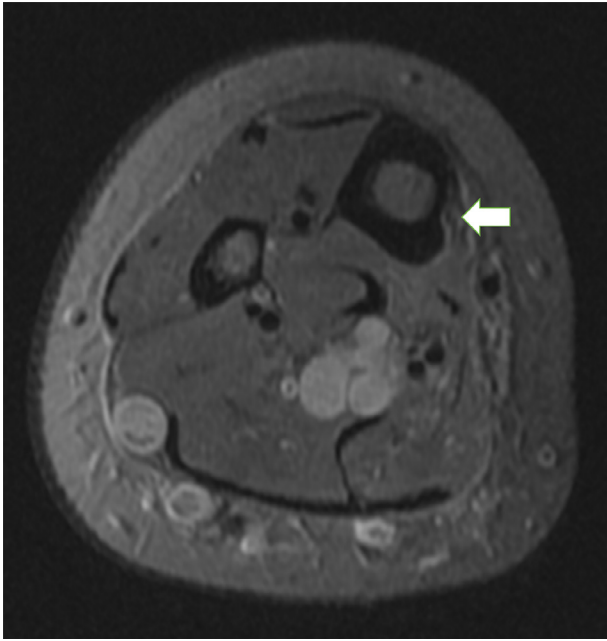


Fig. 2 – A 9-year-old male with neurofibromatosis type 1, a subperiosteal hematoma, and neurofibromas. Axial T2-weighted, fat-saturated MR image obtained 8 months prior to presentation demonstrates a very subtle subperiosteal/periosteal neurofibroma (arrow) with smooth remodeling of the adjacent medial tibial cortex. This neurofibroma was not called prospectively and was only identify after the patients subperiosteal hemorrhage.

hematoma cases. What is different is in fact the presence of subperiosteal focal hemorrhage. To our knowledge, a MPNST primarily arising in a subperiosteal location or a MPNST with subperiosteal hemorrhage have not been reported. Thus, one can cautiously use these findings as signs of probable benignity, which will likely lead to close imaging follow-up rather than more invasive methods, such as open or percutaneous biopsy.

After the initial hemorrhage, 3 clinical sequelae can occur in bland subperiosteal hemorrhage. Spontaneous resolution has been reported in cases who did not have surgical resection. The lesion may persist with calcified periosteum, developing the so-named “subperiosteal cyst.” Finally, rehemorrhage can occur with subsequent enlargement. Those that persist tend to be problematic clinically. Due to the risk of missing any neural elements, a percutaneous needle biopsy should be a secondary consideration. However, this option is the least of the invasive methods and may be of some utility for caregiver/patient reassurance. Surgical biopsy and hematoma evacuation is more invasive but less likely to miss any significant pathology and can be used in patients with persistent pain or other worrisome clinical and imaging findings.

Currently, no follow-up protocols have been described in the literature. The authors propose the following based on the previously described temporal evolution of hemorrhage and certain imaging features. First, it should again be stressed that there have been no reported cases of malignant

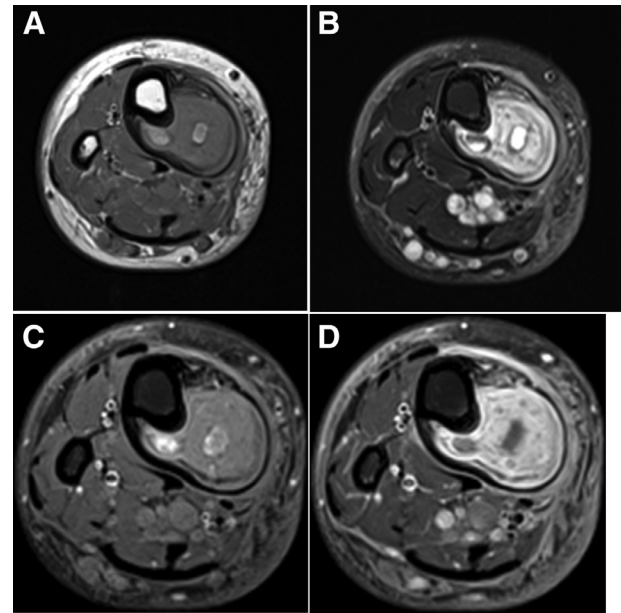


Fig. 3 – A 9-year-old male with neurofibromatosis type 1, a subperiosteal hematoma, and neurofibromas. (A/B) Axial T1-weighted, nonfat-saturated (A) and axial T2-weighted, fat-saturated (B) follow-up MR images at 1 month demonstrates evolution and partial resolution of the superiosteal blood products (A) with increased thick peripheral rim of T2 hyperintensity (B). The periosteal reaction has matured and become more smooth/regular in morphology. Notably, the overall extent of the lesion has not significantly changed. (C/D) Corresponding axial pre- (C) and postcontrast material administration (D) T1-weighted, fat-saturated MR images demonstrate increased thick peripheral enhancement, a finding which can be seen in evolving hematoma.

degeneration presenting as a subperiosteal hemorrhage. We do not suggest that this could not happen, just that it has not been reported. Second, most MPNSTs demonstrate heterogeneous enhancement rather than the peripheral rim enhancement as seen in hematoma. It should not be disconcerting if the peripheral enhancement increases as the hematoma ages, such as in this case. Rather than proceeding to surgical or percutaneous biopsy, the authors suggest watchful waiting with close imaging follow-up, particularly if much of the lesion is hemorrhage. A previous report has demonstrated that a peripheral rim of calcification representing the calcified periosteum develops around 3 weeks after the hemorrhage develops [6]. Thus, we propose radiographs to be obtained at presentation, presuming that a concurrent MRI will be obtained in a child with known NF-1. It would not be surprising if these initial radiographs demonstrate calcified periosteum given the propensity for recurrent subperiosteal hemorrhage. A follow-up radiograph and MRI can be obtained at 3-4 weeks if there is persistent swelling and/or pain. At this time, the lesion should be scrutinized for changes, particularly more erratic enhancement which could suggest malignant degeneration. If the lesion has significantly enlarged without



Fig. 4 – A 9-year-old male with neurofibromatosis type 1, a subperiosteal hematoma, and neurofibromas. Frontal anteroposterior radiograph obtained on the same date as Fig. 3 shows an uplifted and calcified periosteum classically described as a feature of a “subperiosteal bone cyst,” but characteristic of calcifying subperiosteal hematoma.

concurrent increased hemorrhage, then biopsy and/or complete surgical resection should be contemplated. Any additional imaging beyond this point should predominantly be clinically determined although a final short interval follow-up exam at 3-6 months would be reasonable.

Conclusion

Our case represents only the third case in the medical literature of subperiosteal neurofibromas presenting with subperiosteal hemorrhage. As in this case, the initial clinical and imaging findings can be worrisome and indistinguishable from malignant degeneration. However, using what is known about subperiosteal hematomas in NF-1, it should be stressed that initial and follow-up radiographs are important in demonstrating the peripheral calcification of bland subperiosteal thrombus. We propose time zero and around 1-month follow-up radiographs and initial and follow-up MRI imaging. After that time, any additional imaging or intervention should be clinically based although follow-up in 3-6 months would be reasonable.

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