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Clinical Vignette

Angiomatosis of Bone With Localized Mineralization Defect

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CASE PRESENTATION

A 34-YEAR-OLD woman enrolled in a study of the natural history of fibrous dysplasia of bone (FD) at the National Institutes of Health (NIH; 98-D-0145) based on the diagnosis of FD made elsewhere in 1993. At that time, multiple lytic lesions were shown in the left humerus and left femur. The patient complained of intermittent severe pain located in the areas of osteolysis and not related to trauma. Based on the appearance of the radiographs, a diagnosis of FD was made. The lesion in the proximal femur was treated surgically with curettage and insertion of an intramedullary rod. The lesion in the humerus was treated conservatively with occasional immobilization (sling) and nonsteroidal anti-inflammatory drugs for control of pain. The past medical history was significant for hypothyroidism, a subcutaneous lipoma, and an episode of transient but significant thrombocytopenia. In addition, she has had several episodes of significant vaginal bleeding that were evaluated with hysteroscopy and revealed signs of endometrial varicosities (Fig. 1a).

On enrollment in the NIH study in 1999, the physical examination revealed a head circumference at the 90th percentile, high-arched palate, and a café-au-lait spot near the right ankle with a smooth contour ("coast of California"; Fig. 1b). Examination of her two children showed pectus excavatum in both and a nonresolving subcutaneous hemangioma in one child. Assessment of mineral metabolism (serum phosphorus, ionized calcium, parathyroid hormone, vitamin D [25(OH)D and $1,25(OH)_2D$] and urine phosphorus), as well as markers of bone metabolism (serum bone-specific alkaline phosphatase, osteocalcin, and urine N-telopeptide) were all normal. Radiographs showed multiloculated lytic lesions with a honeycomb appearance throughout most of the left humerus (Figs. 1c and 1d). Computed tomography (CT) images through the proximal humerus showed that the multiloculated lesions occupied the medullary cavity (Fig. 1e). The lesions were markedly hyperintense on T2-weighted magnetic resonance (MR) images, and axial images showed fluid levels (consistent with hemorrhage or blood-filled spaces) in several areas (Fig. 1f). Activating GNAS1 mutations associated typically with FD were sought on fresh tissue and stromal cells derived in culture from the biopsy material but were not found.

Histological material from the previous surgery was reviewed and new biopsy specimens were taken from both proximal and distal humeral lesions. No evidence of FD was seen. Abundant, disorganized tangles of irregularly branching blood vessels with arterial, venous, and capillary characteristics (Figs. 2a–2e) were observed in the intertrabecular spaces. Significant variations in size and irregular wall thickness were noted in the abnormal vessels, which were immunoreactive for the endothelial markers CD31 and CD34 (data not shown), as well as for the smooth muscle/pericyte marker α-smooth muscle actin (Fig. 2d). Based on these findings, the diagnosis of skeletal angiomatosis was

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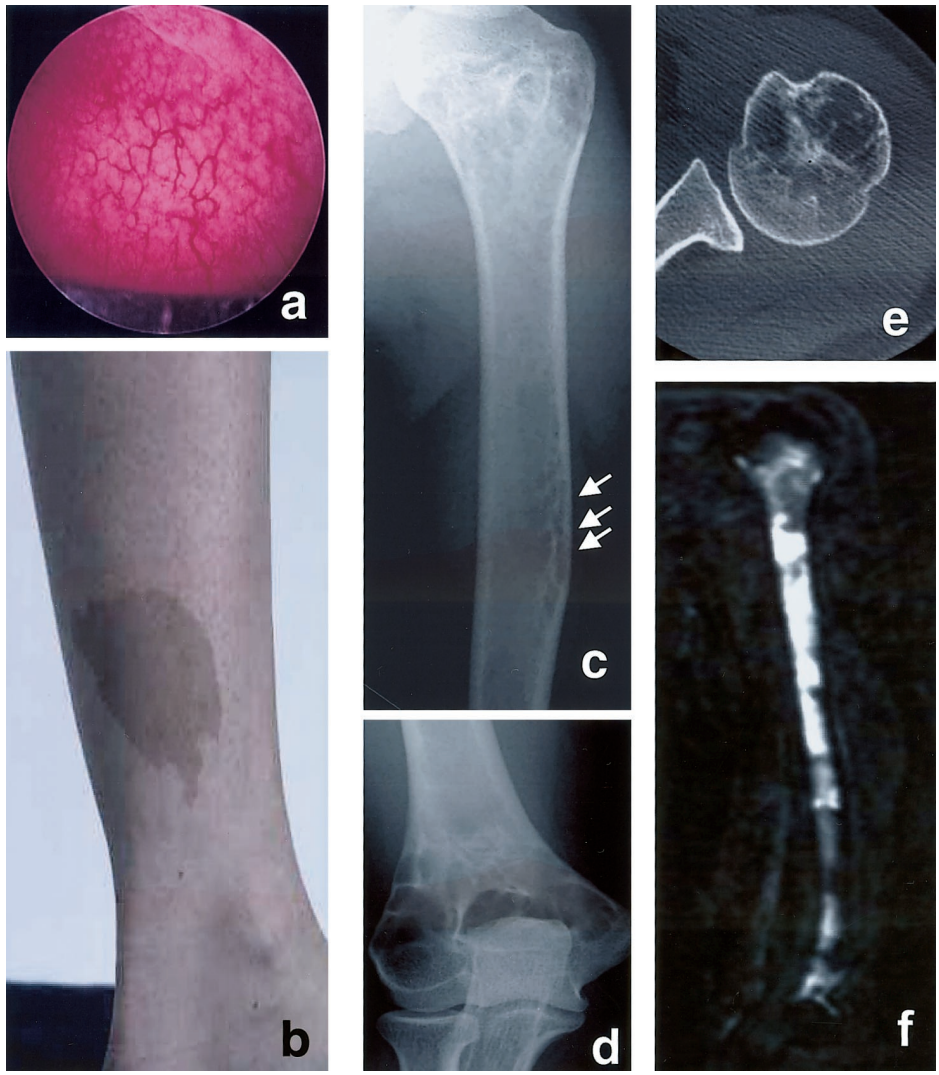

FIG. 1. Clinical images. On hysteroscopy, the endometrium appears (a) highly vascular, suggestive of endometrial varicosities. (b) A café-au-lait spot on the distal lower extremity was significant for smooth borders ("coast of California"), inconsistent with those seen in association with FD and McCune-Albright syndrome. Radiographs reveal multiloculated lytic lesions with a honeycomb appearance in the (c) proximal metaphysis, midshaft (arrows), and (d) distal metaphysis of the left humerus. A CT image through the proximal humerus lesion (e) shows the multiloculated lesions occupying the medullary cavity. (f) A sagittal T2-weighted MR image of the left humerus shows hyperintense marrow replacement throughout.

established. Bone trabeculae interspersed among the angiomatous tissue were predominantly lamellar in structure, with a few coarse ones exhibiting a mixed, lamellar and woven texture. Undecalcified plastic sections were prepared from the new biopsy specimens and stained with von Kossa (Figs. 2e–2j). This showed that intralesional bone trabeculae often were largely or almost completely unmineralized over their full thickness and several hundred microns in length (Figs. 2f–2h). Although they were lamellar in structure, they were not lined by active osteoblasts but were complete with regular arrays of mature osteocytes (Fig. 2h). Large patches of unmineralized osteoid spanning the whole trabecular thickness also were seen to interrupt the continuity of trabecular mineralization (Figs. 2f and 2h). Frequent artifactual trabecular fractures were noted, possibly indicative of the abnormal propensity of the bone tissue to break on specimen handling. The archival, paraffin-embedded material from the initial biopsy had been decalcified and thus obscured the mineralization defect. Not suspecting a mineralization defect, tetracycline labeling was not performed before the second biopsy.

DISCUSSION

Skeletal angiomatosis is a rare condition and may or may not be associated with visceral, cutaneous, and soft tissue lesions.[1] Clinicopathological variants are recognized based on clinical behavior and distribution patterns.[2] In our patient, the association of angiomatosis with thrombocytopenia (Kasabach-Merritt syndrome), a hyperpigmented skin lesion, endometrial varicosities, and a hemangioma in one of her children raises the possibility of a phacomatosis, namely, a Klippel-Trenauney type syndrome.[3] Alternatively, given the association of angiomatosis with a high-arched palate, hypothyroidism, lipoma, pectus excavatum in the children, and the skin lesion, the Bannayan-Riley-Ruvalcaba syndrome also could be considered.[4]

Our case emphasizes the need to entertain many diagnostic considerations in the evaluation of benign-appearing, polyostotic skeletal lesions. These include FD, enchondromatosis, Langerhans cell histiocytosis, unusual infections, neurofibromatosis, and angiomatosis.[5] These are, in our experience, often misdiagnosed as FD. However, careful

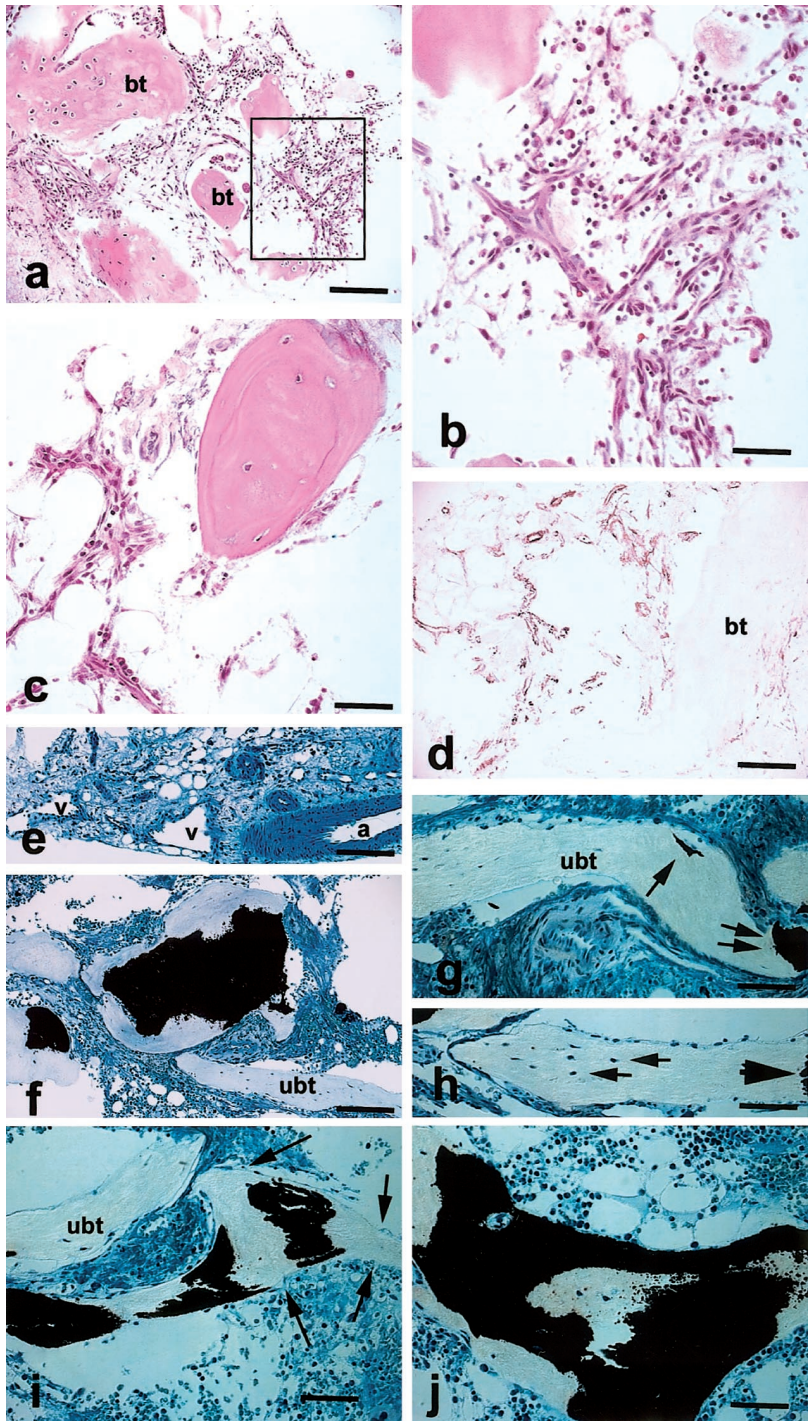

FIG. 2. Histological features. (a–e) Angiomatous nature of the bone lesion. (a–c) Disorganized tangles of irregularly branching blood vessels occupy the marrow spaces between bone trabeculae (detail of region boxed in panel a) and (d) are immunostained by α-smooth muscle actin. (e) Vessels of arterial and venous type with irregular walls are closely intermingled. (f–j) Undecalcified plastic sections stained with von Kossa showing the localized mineralization defect in the intralesional bone trabeculae. (f–i) Note that some trabeculae are unmineralized almost completely across their full thickness and over several hundred microns of their length or (i, arrows, and j) show large patches of unmineralized osteoid interrupting the continuity of matrix mineralization. Arrays of mature osteocytes are seen within the trabeculae (arrows in panel h). Arrow in panel g points to an isolated spot of mineral within an otherwise unmineralized trabecula, and double arrows point to the boundary of the mineralized portion of the trabecula (also thick arrow in panel h). bt, bone trabeculae; ubt, unmineralized bone trabeculae. (a, d, e, and f) Bar = 250 m; (b, c, g, h, i, and j) Bar = 125 m.

histological study and the use of current techniques for showing relevant GNAS1 mutations are invaluable in establishing the diagnosis of FD. In addition, in this case, several aspects of the clinical evaluation could have led to the correct diagnosis. For example, the skin lesion did not fulfill the criterion of the so-called "coast of Maine" border and the laboratory studies failed to show a significant elevation in markers of bone remodeling, a usual finding in FD.[6]

The use of undecalcified plastic embedding of the biopsy material enabled us to recognize a severe, localized mineralization defect in the bone trabeculae, which were interspersed with the angiomatous tissue (Figs. 2e and 2f). Perhaps owing to the fact that this technique is not used routinely in surgical pathology departments, this has not, to the best of our knowledge, been noted before in benign vascular lesions of bone. We feel that this finding is of interest in view of the fact that most of the tumors associ-

ated with oncogenic osteomalacia are either of vascular nature or richly vascularized.[7] The general paradigm reads that such tumors systemically secrete a factor (recently proposed to be fibroblast growth factor 23 [FGF-23][8]) capable of diminishing renal phosphate reabsorption. In light of this, we feel it was interesting to note that a bone vascular tumorlike lesion may be associated with a type of localized osteomalacia in the absence of systemic changes of skeletal mineralization or mineral metabolism. This lesional osteomalacia may generate (as it was likely the case in our patient) localized bone pain through trabecular microfractures and weakening of the bone. Recently, we have observed a case of a phosphaturic tumor of bone with oncogenic osteomalacia in which a similar local mineralization defect was observed within the lesion (data not shown). These observations raise the interesting possibility that some vascular lesions (phosphaturic tumors) may exert a generalized adverse influence on skeletal mineralization via a systemic hormonal effect, and others may only impair local mineralization as a paracrine effect, perhaps of the same factor(s) putatively produced by the phosphaturic tumors—a hypothesis that remains to be tested.

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REFERENCES

1. Murphey MD, Fairbairn KJ, Parman LM, Baxter KG, Parsa MB, Smith WS 1995 From the archives of the AFIP. Musculoskeletal angiomatous lesions: Radiologic-pathologic correlation. Radiographics **15:**893–917.
2. Dorfman HD, Czerniak B 1998 Vascular lesions. In: Dorfman HD, Czerniak B (eds.) Bone Tumors. Mosby, Inc., St. Louis, MO, USA, pp. 747–761.
3. Atiyeh BS, Musharrafieh RS 1995 Klippel-Trenaunay-type syndrome: An eponym for various expressions of the same entity. J Med **26:**253–260.
4. Gorlin RJ, Cohen MM Jr, Condon LM, Burke BA 1992 Bannayan-Riley-Ruvalcaba syndrome. Am J Med Genet **44:** 307–314.
5. Resnick D, Greenway GD 1996 Tumors and tumor-like lesions of bone: Imaging and pathology of specific lesions. In: D Resnick (ed.) Bone and Joint Imaging. Saunders, Philadelphia, PA, USA, pp. 991–1063.
6. Collins MT, Shenker A 1999 McCune-Albright syndrome: New insights. Curr Opin Endocrinol Diabetes **6:**119–125.
7. Park YK, Unni KK, Beabout JW, Hodgson SF 1994 Oncogenic osteomalacia: A clinicopathologic study of 17 bone lesions. J Korean Med Sci **9:**289–298.
8. White KE, Evans WE, O'Riordan JL, Speer MC, Econs MJ, Lorenz-Depiereux B, Grabowski M, Meitinger T, Strom TM 2000 Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. Nat Genet **26:**345–348.

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