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Review Article

Bizarre parosteal osteochondromatous proliferation or Nora's lesion affecting the extremities: A concise update

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ABSTRACT

The bizarre parosteal osteochondromatous proliferation or Nora's lesion is an unusual clinical entity that presents with localized swelling and pain. The characteristic radiological appearance includes a cluster of variably calcified lesions adjacent to a particular bone. However, it does not necessarily have direct continuity with its medullary region. The etiopathogenesis of this disorder is not yet fully understood. Various other lesions require careful exclusion and the use of advanced imaging modalities to supplement the diagnosis. The final diagnosis of the lesion, however, is based on the histopathological basis. However, these lesions are reported as sporadic reports or small series in the literature and are also discovered in areas other than the common locations in hands and feet. The recent research aims to throw more advanced knowledge into their causation, including genetic etiology. The symptomatic lesions may require excision for clinical relief, but recurrence is not uncommon. The future research, and preferably multi-center collaboration, is required for more insight into their comprehensive nature and clinical spectrum. A brief and crisp update of the articles published in the past 10 years describing bizarre parosteal oseochondromatous proliferation in the extremities is presented here for educational purposes for orthopedists and generalists alike.

Keywords: Benign tumor, Bizarre parosteal osteochondromatous proliferation, Diagnosis, Extremities, Nora's lesion

INTRODUCTION

Bizarre parosteal osteochondromatous proliferation (BPOP) was first described in 1983 by Nora *et al.* with cases involving hands and feet.[1] Therefore, this clinical entity is also called Nora's lesion. Localized swelling and pain are the most common presentations. The radiographic findings include dense and mineralized lesions adjacent to an uninvolved bone. Hand and feet are the most commonly involved sites, but other anatomical locations have also been reported over the years. Various disorders pose diagnostic challenges and need to be kept in the working diagnoses [Table 1]. However, osteochondroma is the most common resembling lesion that must be excluded from the study. BPOP usually bears no connection with the adjacent bone. BPOP is considered a locally aggressive benign tumor that usually affects the age range of 8–74 years, as mentioned in the literature. The involvement in the younger age group is not infrequent. There were three cases (between ages 2 and 12 years) in a recent series.[2] Reports of involvement in the

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Table 1: The disorders resembling bizarre Parosteal Osteochondromatous Proliferation (Nora's lesion) or differential diagnoses.

Atypical exostosis or Osteochondroma, atypical variant like extra-skeletal osteochondroma
Turret exostosis
Florid reactive periostitis ossificans
Heterotrophic ossificans traumatica
Myositis ossificans
Parosteal osteosarcoma
Surface chondroma, for example, periosteal chondroma
Cortical irregularity
Trevor disease (Trevor-Fairbank disease) or dysplasia epiphysalis hemimelica

age group beyond above-mentioned limits were also noted during the literature search for this article, with two cases of age 3 years reported [Table 2]. The age of involvement is thus wider ranging in cases of BPOP. A retrospective analysis of cases of BPOP from the Scottish Bone Tumor Registry from 1983 to 2009 revealed only 13 cases with no gender predilection (six males and seven females) and a wide age range (13–65 years). Twelve of these cases involved hands and feet and one case involved tibial tuberosity.[3] A previous history of trauma was noted only in two cases. There was no metastasis associated, but recurrence in the range of 50% was noted.

The typical microscopic features are cartilage cell pleomorphism, spindle cells, different stages of bone maturation, and the presence of calcification without cellular atypia.[3,4] The bone trabecular pattern seen in the pathological specimens of BPOP lesion is characteristically stained blue with hematoxylin and eosin. This purplish-blue mineralization of cartilaginous tissues known as "blue bone" is one of the characteristic features of BPOP. The histologic variety of these lesions as described in a large series indicates that these lesions are composed of bone, cartilage, fibrous tissue and "blue bone," but the amount of each tissue varies and a few show focal "blue bone" only.[4] Research on the molecular level is undergoing to differentiate between the osteochondroma and BPOP and initial findings indicate different genetic regulatory mechanisms involved.[5] Environment and injury are supposed to be linked with their formation, whereas extracellular matrix composition dictates different characteristics of both the lesions. To reach appropriate diagnosis, a thorough clinical, radiological, and histological evaluation is required to rule out osteochondroma or exostosis.[6]

MATERIALS AND METHODS

The articles listed in PubMed and PubMed Central were searched from 20 to 25 April 2022 and relevant articles describing BPOP in musculoskeletal tissues were noted. The lesion involving extremities was included in the study, while those involving other anatomical areas like the mandible or spine were excluded from the study. The search terms were "BPOP" and "Nora's lesion" with Boolean operators AND "musculoskeletal" or "extremity." The articles were read in detail for key characteristics such as location, clinical problem, radiological features, and treatment, along with key demographic details of the cases, including age and gender. The articles in the past 10 years were filtered during the search process and those published before 2011 were not included in the study.

Similarly, articles in non-English languages were excluded from the study. PubMed and PubMed Central were chosen over others as they are popular and widely accessed portals. Including other platforms such as Scopus, Embase, CINAHL, or Ovid would have resulted in too many articles to be included in a standard review article and would have exceeded the word limit for the same.

HAND

Hand has been traditionally considered the most common location of BPOP. Differentiation of hand BPOP lesions should be done with osteochondroma-like lesions.[7] Middle phalanx has been found to be commonly involved in four cases followed by metacarpals in three cases, and proximal phalanx in one case. BPOP may be a rare lesion, but the cortical and medullary connections in advance imaging will differentiate osteochondroma from BPOP in most cases. In an unusual case of BPOP involving a second metacarpal, wide excision and reconstruction with non-vascularized fibula autograft were performed along with metacarpophalangeal joint replacement. No complication or recurrence was noted in 2 years of follow-up.[8] In another report of two cases of metacarpal involvement, one of the cases had a recurrent lesion, which was later managed by ray amputation.[9] Two cases in a series were located in the proximal phalanx of the middle finger and second metacarpal, respectively, as hard bony swelling and were excised, leading to good clinical results.[10] Flecks of calcification within a broad-based mineralizing lesion over proximal phalanx were noted without cortical flaring, osteolysis, and periosteal reaction as a typical feature of BPOP.[11] Middle finger involvement in a 4-year-old girl was reported with swelling and pain on the radial aspect along with a calcified lesion.[12] The mass was non-tender and did not affect the movement. A well-defined nodular lesion about 2 cm at the base of the middle phalanx was noted on magnetic resonance imaging (MRI). Wide excision of the bluish mass with no area of necrosis was confirmed as BPOP in histopathological studies. A case of a left index finger lump was noted that was increasing in size and leading to pain and restricted motion. A radiolucent lesion

Table 2: A few reported singular cases with key clinical findings.

Authors	Age (in years)/Gender	Location	Clinical features	Duration of symptoms	Treatment	specific features
Pal *et al.*	21/M	R anterior knee	Progressive swelling, flexion limitation	1 year	EB	Lesion engulfing PT which was intact
Takahashi *et al.*	54/M	L femur	Pain and mass	3 months	EB	Medial femur mass calcified
Kershen *et al.*	37/F	R tibia posteromedial aspect	Night pain, tender mass	1 year	Biopsy	-
Matsui *et al.*	58/F	L wrist ulnar aspect	Wrist pain	3 months		Initially managed by crystal arthropathy with steroid injection
Lin *et al.*	48/M	L, Volar aspect of the wrist	Growing mass	1 year	EB	
Rothenberg *et al.*	37/F	L upper humerus	Painless mass	2 weeks	EB	Mass noted after strenuous workout
Kumar *et al.*	4/F	R middle finger middle phalanx	Pain, swelling	5 months	Wide excision	Increase in size for the last 2 months
Salna *et al.*	35/F	L index finger, Base of middle phalanx	Progressive tender lump, decreased finger motion	Several months	Excision followed by recurrence and repeat excision	History of laceration at the same site
Lynch *et al.*	35/M	R index finger	Painless mass	-	EB	Mass noted in routine physical examination
Khatri *et al.*	50/F	R index metacarpal	Progressive swelling	1 year	Core biopsy confirmation followed by wide excision, fibular gift and MCPJA	-
Mahajan *et al.*	37/F	L great toe plantar medial aspect	Non tender mass	1 year	Wide excision	Multi-lobulated mass with pseudo-capsule
Yao *et al.*	57/F	R third metatarsal	Pain, swelling, mass	1 month	EB	CT showed stress fracture with bone scan increased uptake
Rottler *et al.*	49/M	R ankle, talocalcaneal region	Swelling tenderness	10 weeks	An open biopsy followed by wide resection and arthrotomy of ankle and sinus tarsi	Initially treated as tenovaginitis of peroneal tendons
Takeda *et al.*	46/M	L Hallux plantar sesamoid	Painful mass	6 years	Resection with host sesamoid bone	Mass noted 23 years ago
Mohammad *et al.*	60/M	R second toe	Painful bluish, bulbous subungual swelling	-	EB	-
Hussain and Arif	3/M	R middle finger middle phalanx	Valgus deformity and swelling	2 years	EB	Deformity progressing from last 3 months
Bhalla *et al.*	10/M	R Popliteal fossa	Pulsatile mass	-	Resection and pseudoaneurysm repair	Exostotic lesion posterior femur on CT
Colangeli *et al.*	3/M	L First metatarsal	non-tender mass	-	Conservative	Associated CIPA

M: Male, F: Female, L: Left, R: Right, EB: Excisional biopsy, PT: Patellar tendon, MCPJA- Metacarpophalangeal joint arthroplasty, CT: Computerized tomography, CIPA: Congenital insensitivity to pain and anhydrosis

and peripheral calcification were seen on radiographs.[13] Ultrasonography (US) revealed a well-circumscribed mass lateral to flexor tendons and a calcified encapsulated mass adherent to the middle phalanx. Six months later, recurrence was reported after re-exploration of the tender lump at the previous site with restricted proximal interphalangeal joint motion. Repeat exploration and marginal excision one more time led to healing without recurrence. The spectrum of the lesion shown in this case was consistent with progressive cartilage proliferation resembling a benign chondroma. To add to the diagnostic dilemma, the presence of a central osseous component with a peripheral cartilaginous element resembles an acquired osteochondroma.

Another reported case had a middle phalanx exostosis. After few months, increased swelling and movement restriction revealed a lesion over the middle phalanx extending up to the proximal phalanx, and a fifth ray amputation was the definitive treatment. This case underlines the locally aggressive behavior of BPOP in rare instances. An index finger painless mass, in a different case, was surgically removed and disordered spindle cell proliferation without a cartilage cap was noted with a final diagnosis of BPOP.[14] In another case, with a lesion on the middle phalanx of the ring finger, the central continuity of the lesion with the underlying bone marrow was seen, which was similar to that seen in osteochondroma. This case also had an inversion of the chromosome 7 [inv(7)(q22q32)].[15]

UPPER EXTREMITY

Although the hand is a frequent site for BPOP, other uncommon areas are now increasingly reported with a various presentations. Starting from proximal to distal locations in the upper extremity, one case each involving the proximal humerus and the ulna diaphysis was reported, respectively. Distal ulna, however, was most commonly involved in four separate cases. The age range involved 8–58 years; the youngest being an 8-year-old girl and the oldest case aged 58-year-old female. A painless mass due to a fixed, firm, and tender lesion at the upper humerus (anterolateral cortex) without movement restriction was reported. A well-circumscribed, radio dense mass without cortical continuation, no cartilage cap or soft-tissue component was noted on radiographs and MRI.[16] The BPOP was the final diagnosis. Ectopic calcification near the distal radioulnar joint region in a 58-year-old female with pain and restricted pronation and supination movement was not relieved despite steroid injection given locally.[17] Computerized tomography (CT scan) revealed a mass originating from the distal ulna without continuity with the medulla of the bone. The lesion with a layer of cartilage cap was excised *en bloc* with the capsule, followed by decortication of the underlying bone and the histology confirmed the diagnosis of BPOP. In another report, the lesion presented as a painless growing mass arising from the volar surface of the left distal ulna.[18] No pressure signs or restricted motion were associated despite a mild increase in size. Calcified mass seen on radiographs was also confirmed on MRI that showed multiple calcified areas without any connection to the ulna. An excision biopsy was done and revealed BPOP. One more report of distal ulna involvement with a history of injury in a 22-year-old male patient presented with a painless wrist mass.[19] In a different case of distal ulna lesion in an 8-year-old girl, translocation of t(1;17) (q32;q21) was demonstrated. The report also advocated using cytogenetics for rapid and accurate diagnosis in difficult cases.[20] An interesting case of recurrent forearm BPOP after a previous excision and aggressive-looking features over the ulna was reported. The lesion also resulted in the erosion of adjacent radius bone with aggressive-looking features. This case highlights the importance of careful differentiation of BPOP from malignant lesions as the course of treatment and prognosis is different.[21] The future research shall throw more light on the molecular etiology of BPOP or similar lesions. Jmjd3 is reported to affect bone development and osteoarthritis and some work has suggested the involvement of the Jmjd3/p16^{ink4a} pathway essential for the causation of BPOP-like lesions in mice experiments.[22] Jmjd3 is a H3K27me3 methylase and is important for the normal development and differentiation of stem cells. Jmjd3 counteracts polycomb-mediated transcription repression and deletion of Jmjd3 in chondrogenic cells is found to result in BPOP-like lesions in mice experiments. Jmjd3 thus seems to be an important pathway (through p16^{ink4a}) to through light on enigmatic bone-forming mechanisms in BPOP and other lesions in the future.

FOOT

A total of ten cases were reported affecting feet and presented with the myriad presentations. Toes were most frequently involved, followed by metatarsals in four and two cases, respectively. All other regions, including the talocalcaneal area, heel, and sesamoid bone, had a single case each been described. A progressive growing lesion in a young adult female with a non-tender and non-mobile mass on the posteromedial aspect of the left great toe was reported.[23] Proliferated fibrous tissues, cartilage and irregular enlarged clumps of nucleated and bizarre chondrocytes indicating BPOP were noted in the biopsy. In one of the cases from a series of four cases (all others with hand involvement), a fusiform wide-based ossified mass on the plantar surface of the third right toe was excised and finally diagnosed as BPOP.[24] An interesting case of foot swelling in the right foot third metatarsal with pain that increased on walking revealed a non-mobile mass. CT scan showed a neck fracture of the third metatarsal with osteolysis at the fracture site, after

which bone scintigraphy showed increased tracer uptake suggesting a stress fracture. The lesion was excised and diagnosed as BPOP on histopathology, thus highlighting the rare coexistence of stress fracture with BPOP.[25]

A case of a 10 weeks old, atraumatic right ankle swelling was treated for probable arthritis and tenosynovitis.[26] The radiograph showed small spotted demineralization and osteolysis near the talus and calcaneum, along with joint effusion and subcutaneous edema. CT scan also corroborated similar findings and samples from medial talus and peritalar soft tissues were taken. Nora's lesion was found, following which complete resection through arthrotomy of lateral ankle and sinus tarsi was done.

Medial sesamoid of the great toe as the site of origin of BPOP was recently reported and managed with *en bloc* excision and no recurrence was noted in the 5-year follow-up.[27] Another report describing a rare location of sesamoid bone of great toe presenting as a painful mass making daily walk difficult was later managed by biopsy diagnosis and surgical resection.[28]

Another case with chronic plantar heel pain had a diagnostic dilemma with a provisional diagnosis of plantar fasciitis and parosteal osteosarcoma. She had clinical improvement and complete resolution of symptoms at an 18-month follow-up after a bone biopsy that also confirmed BPOP.[29] Unusual presentation in the form of recurrent subungual exostosis in a child's foot was reported.[30] The lesion had a high recurrence rate and typical histological findings included an enchondral ossification zone with an unusually mineralized cartilaginous matrix "blue bone." In a different case, a mass over the left foot's second metatarsal was hyperintense with extensive bone marrow edema on MRI and showed less fibroblastic tissue and cartilaginous pleomorphism. This case underlined the importance of maturation phenomena noted in histological specimens of parosteal cartilaginous lesions.[31]

A recurrent toe lesion has also been reported as a nagging problem and a therapeutic challenge.[32] In another case, a lesion presenting and mimicking gloms tumor as painful bluish bulbous swelling of the right second toe was reported and radiographs showed a calcified lesion near a tuft of terminal phalanx and MRI showed a low signal nodule on T1 and T2 in subungual area.[33] The case underlines the importance of overlapping clinical features of glomus tumor and BPOP in rare instances that require proper differentiation.

LOWER EXTREMITY

A total of five cases arising near distal femur, patella, fibula, leg, and proximal tibia are reported. A diffusely calcified mass adjacent to the medial cortex of the distal femur in a different patient showed an absent medullary connection and the lesion was excised to reveal the BPOP on histopathology.[34] One case presenting as a growing lesion at the lower pole patella after the skeletal maturity with progressive swelling in a 21-year-old male was reported.[35] The swelling seemed fixed to the patella and moving along with it and the mass incorporated the patellar tendon entirely except for a narrow cleavage. Thin cartilage layer and irregular lamellar bone were found without marrow, periosteum element, or neoplastic cellular changes. This case snippet highlights suspecting BPOP in cases with atypical features related to an exostosis like growth beyond skeletal maturity. Pathological studies in another case of fibula head lesion in a young man were done to identify layers of the lesion and showed intense and diffuse immunohistochemical expression to S-100 protein, a previously unreported feature.[36] This case also underlined trauma; however, minor, as an important factor in developing these lesions. In a series of five cases, one of the cases involved proximal tibia extending posteriorly and superiorly across the knee joint, leading to a flexion knee deformity.[37] Wide resection of the mass with proximal tibia mega-prosthesis was done along with resection of part of the fibula. A posteromedial painful right leg mass in a young female was noted without a history of any antecedent injury.[38] Tender, firm, and non-mobile mass was seen clinically, and the radiograph showed more than a 3 cm area of amorphous calcification without bony communication. MRI revealed an aggressive and expansile lesion, the incisional biopsy of which revealed BPOP. The growth of a lesion after skeletal maturity is not a typical feature of osteochondroma.

UNCOMMON PRESENTATIONS

A recent report presented BPOP involving the hands and feet region and causing angular deformities. Middle finger valgus deformity along with hard bony middle phalanx swelling was noted in a 3-year-old.[39] Furthermore, there was another lesion at the medial aspect of the second toe of the right foot, also causing valgus deformity. Both lesions were managed by surgical excision. In another case, a lesion in the second interspace presenting as splay foot deformity was also reported highlighting diagnostic workup in subtle splay deformity cases.[40] In the first of such reports, complete regression of a calcified lesion adjacent to the first metatarsal bone was reported and confirmed as Nora's lesion on biopsy. The wait and watch approach resulted in complete remission over 2 years in that particular case of the first metatarsal lesion in a 3-year-old child with hereditary sensory and autonomic neuropathy Type IV (HSNA IV) with congenital insensitivity to pain and anhidrosis.[41] This report suggests that the BPOP might be a reactive process. One unusual case of the left groin mass arising from the iliac wing with intra-abdominal extension was also noted displacing abdominal content anteromedially in a newborn.[42] Biopsy of resected

specimen done at 5 months of age revealed BPOP and clinical recovery. In another case, a 10-year-old patient was reported with a popliteal pseudoaneurysm on MRI and a palpable pulsatile mass in the upper popliteal fossa.[43] The CT angiogram also confirmed a pseudoaneurysm adherent to an exophytic mass in the posterior femur, which was then resected, and the vascular lesion repaired. The diagnosis of BPOP was made on the histopathological report to make the case unusual based on age and location.

CONCLUSION

The BPOP or Nora's lesion is an enigmatic entity that is sporadically reported in the medical literature with unusual clinical presentation. The proper understanding of the disorder may be attained by working knowledge of the condition and more robust work in the future is required to understand their comprehensive clinical behavior and pathogenesis. Swelling, pain, and radiological evidence of variably calcified mass along the cortical bone is the typical feature and histological confirmation (with characteristic "blue bone" appearance) is crucial for the diagnosis.

AUTHORS' CONTRIBUTIONS

GSD and ISD did the conception and the literature search. NA wrote the first draft and TP wrote the final draft. GSD approved the final draft. All authors have critically reviewed and approved the final draft and are responsible for the manuscript's content and similarity index.

ETHICAL APPROVAL

The ethics committee approval was not required for this research paper as there is no direct patient involvement in this review.

DECLARATION OF PATIENT CONSENT

Patient's consent not required as there are no patients in this study.

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CONFLICTS OF INTEREST

There are no conflicting relationships or activities.

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