

Study of Multimodality Imaging Features of Brown Tumor or Osteitis Fibrosa Cystica

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Abstract

Introduction

Brown tumor, also known as osteitis fibrosa cystica, is a rare but significant manifestation of hyperparathyroidism characterized by focal bone lesions resulting from excessive osteoclastic activity. Despite its rarity, Brown tumor poses diagnostic challenges due to its varied clinical presentations and radiographic features, often mimicking other bone lesions such as giant cell tumors or metastatic disease.

Material and Methods

In this study, we present a retrospective analysis of 6 cases of Brown tumor diagnosed and managed at our institution over a 12 months period from April 2022 to April 2023. Our objectives are to delineate the diverse clinical manifestations of Brown tumor, discuss diagnostic modalities utilized, treatment strategies employed, and evaluate patient outcomes. Laboratory changes were reanalysed using two-sided paired t-tests on the six published paired observations.

Results

Five out of our six patients were females. Also 4 out of our 6 patients were under the age of 25. 3 patients presented to us with multiple lytic lesions and other 3 patients had solitary lesions. 1 patient out of 6 presented to us with pathological fracture. Only 2 out of the 6 patients had a positive sestamibi scan but Ultrasonography (USG) of the neck and MRI of the neck showed the presence of parathyroid adenoma in all the cases. Following parathyroidectomy, mean serum PTH and calcium levels decreased significantly (two-sided paired t-tests: $p = 0.0085$ and $p = 0.0293$, respectively). Changes in serum phosphorus and alkaline phosphatase were not statistically significant ($p = 0.3708$ and $p = 0.0903$, respectively). Mean VAS scores decreased from 67 to 24; statistical significance could not be assessed from the reported summary data.

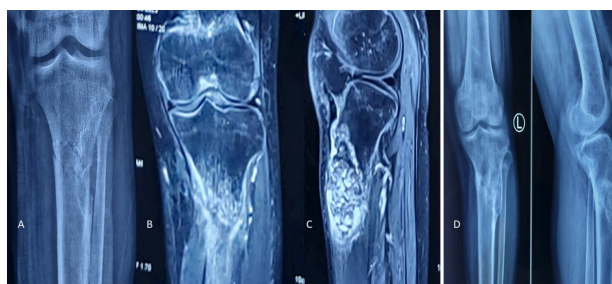


Figure 1: Case of 23 year male patient with brown tumor and lytic lesion with pathological fracture in proximal tibia: A) X-ray of knee with leg showing lytic lesion in proximal tibia with pathological fracture. B) T2 Coronal MRI Images showing hyperintense cystic components. C) T2 Sagittal MRI Images showing cystic components with fluid-fluid levels on anterior cortex of proximal tibia. D) X-ray of knee with leg showing complete union of pathological fracture without any operative intervention other than parathyroidectomy

Conclusion

When radiographic evidence of a lytic lesion and hypercalcemia are present, Brown tumor should always be considered in the differential diagnosis. Brown tumor has a distinctive imaging appearance, with solid components displaying intermediate to low intensity on T1- and T2-weighted images, while the cystic components appear hyperintense on T2-weighted images and exhibit fluid-fluid levels. MRI of the neck corroborates the ultrasound findings and detects parathyroid adenomas as hyperintense nodes on T2-weighted images. Parathyroidectomy yields excellent results, enabling conservative management of lytic lesions.

Keywords: Brown tumor, parathyroidectomy, sestamibi scan, parathyroid adenoma, osteitis fibrosa cystica

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Introduction

Brown tumors are non-neoplastic lesions resulting from abnormal bone metabolism in hyperparathyroidism (1). They have been described in both primary and secondary hyperparathyroidism as resulting from an imbalance of osteoclastic and osteoblastic activity with bone resorption exceeding the bone formation (1).

Brown tumor, also known as osteitis fibrosa cystica, is a rare but significant manifestation of hyperparathyroidism characterized by focal bone lesions resulting from excessive osteoclastic activity. Historically associated with advanced primary hyperparathyroidism, Brown tumor is now increasingly recognized in the context of secondary and tertiary hyperparathyroidism, particularly in patients with chronic kidney disease (2).

Primary hyperparathyroidism (PHPT) is a systemic disease caused by lesions of the parathyroid gland (such as parathyroid adenoma, parathyroid hyperplasia, and parathyroid carcinoma) (3) PHPT leads to the synthesis and secretion of parathyroid hormone (PTH) and causes calcium, phosphorous and bone metabolism disorders. The main clinical manifestations are bone diseases with increased bone resorption, hypercalciuria-induced urinary calculi, hypercalcemia, and hypophosphatemia (4). Despite its rarity, Brown tumor poses diagnostic challenges due to its varied clinical presentations and radiographic features, often mimicking other bone lesions such as giant cell tumors or metastatic disease (5). Additionally, the management of Brown tumor requires a multidisciplinary approach involving endocrinologists, radiologists, surgeons, and nephrologists to address the underlying hyperparathyroidism and its associated complications (6). To the best of our knowledge, the literature on Brown tumor is limited to case reports and small case series.

In this case series, we present a retrospective analysis of 6 cases of Brown tumor diagnosed and managed at our Institution Gujarat Cancer and Research Institute over a 12 months period from April 2022 to April 2023. Our objectives are to delineate the diverse clinical manifestations of Brown tumor, discuss diagnostic modalities utilized, treatment strategies employed, and evaluate patient outcomes. Through this series, we aim to contribute to the existing body of literature on Brown tumor. Additionally, we seek to highlight the importance of early recognition and comprehensive management of hyperparathyroidism to mitigate the morbidity associated with Brown tumor and improve patient outcomes.

Materials and Methods

Most patients present with pain and swelling at one or multiple sites, and many also present with pathological fractures. We conduct a thorough investigation for cystic lytic lesions in each patient, including serum calcium, phosphorus, parathyroid hormone (PTH), alkaline phosphatase levels, and localized X-rays and magnetic resonance imaging (MRI).

Laboratory tests revealed elevated levels of serum calcium and PTH, which are characteristic of hyperparathyroidism. We evaluated serum phosphorus levels, which may be low in primary hyperparathyroidism and elevated in secondary hyperparathyroidism. Serum alkaline phosphatase levels which may be elevated due to increased bone turnover. In this study we present a retrospective analysis of 6 cases of Brown tumor diagnosed and managed at our Institution over a 12 months period from April 2022 to April 2023.

We were able to identify this patients based on their elevated PTH levels and deranged serum calcium, phosphorus and alkaline phosphatase with cystic lytic lesions. Also serum vitamin D3 was checked upon. And CT-Scan of paranasal sinus, thorax, abdomen and pelvis of all the patients was performed to find out any other sub-clinical lesions which were present in the body. Detailed imaging of all the involved parts was done. Imaging studies play a crucial role in the localization and characterization of parathyroid adenomas, which are the most common cause of primary hyperparathyroidism.

All the patients were then investigated with Ultrasonogram (USG) of Neck, MRI Neck, and Technetium-99m Sestamibi Scan (MIBI Scan). These imaging studies are often used in combination to localize parathyroid adenomas accurately and guide surgical intervention, leading to improved outcomes for patients with primary hyperparathyroidism.

These patients were then referred to our Head and Neck Department, for parathyroid management and our bone lesions were managed conservatively till then. One patient which had pathological fracture was also managed conservatively (Table 1). Parathyroidectomy was done in all the patients; postoperative laboratory values were recorded. Also

vitamin D3 deficient patients were given vitamin D3 supplementation in the form of 60'000 IU per week for 8 weeks followed by 60'000 IU monthly for 6 months.

Laboratory changes were reanalysed using two-sided paired t-tests on the six pre- and

humerus. No periosteal reaction, calcification, or abnormal soft tissue was observed.

- Magnetic Resonance Imaging (MRI): Solid components were intermediate to low intensity on T1- and T2-weighted images, while the cystic components were hyperintense on T2-weighted

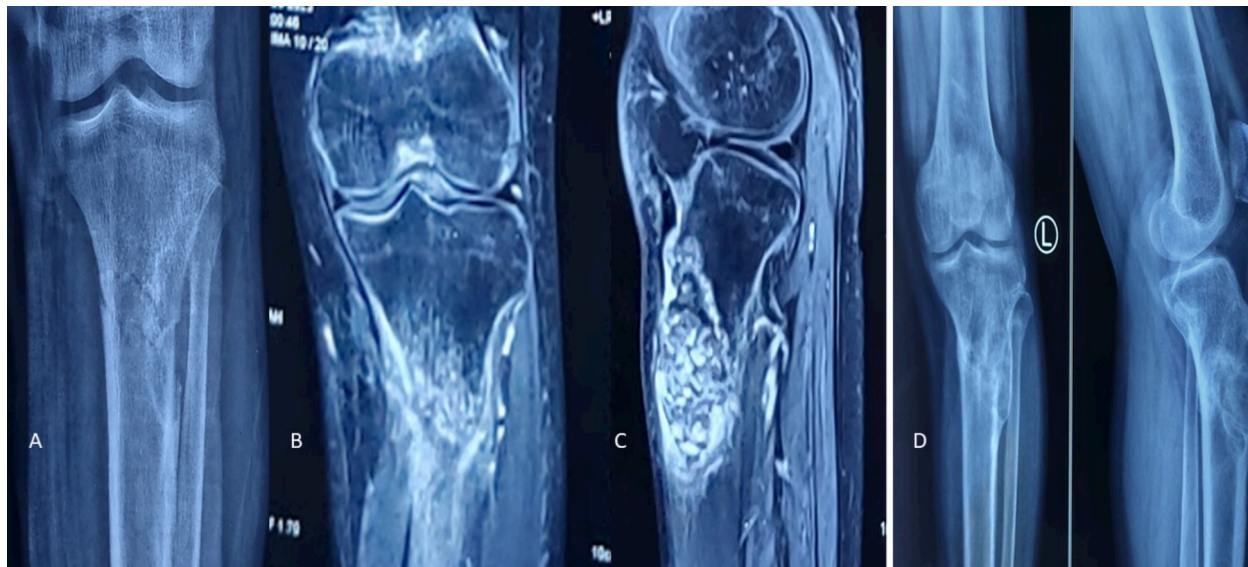


Figure 1. Case of 23 year male patient with brown's tumor and lytic lesion with pathological fracture in proximal tibia:

A) X-ray of knee with leg showing lytic lesion in proximal tibia with pathological fracture.

B) T2 Coronal MRI images showing hyperintense cystic components.

C) T2 Sagittal MRI Images showing cystic components with fluid-fluid levels on anterior cortex of proximal tibia

D) X-ray of knee with leg showing complete union of pathological fracture without any operative intervention other than parathyroidectomy

postoperative values in Table 1. Unadjusted p-values are reported; $p < 0.05$ was considered statistically significant. VAS scores were summarised descriptively because individual paired scores were unavailable. Postoperative X-rays documented sclerosis, reduction in lytic cavity size and subperiosteal bone resorption. Healing of the pathological fracture was monitored.

images and showed fluid-fluid levels.

Blood Investigations:

The patient's serum PTH concentration was 1133 pg/mL (Table 1). Calcium was 15.9 mg/dl and serum phosphorus was 1.62 mg/dl. Serum alkaline phosphatase was also very high 2153 (U/l). Due to these deranged values parathyroid adenoma was suspected and so Sestamibi scans, USG and MRI of the neck were done. Also computed tomography scan of paranasal sinus, thorax, abdomen and pelvis was done to find any other lesion in the body.

Ultrasonography of Neck: It showed presence of 3.5 cm x 2.5 cm x 1 cm nodes behind the thyroid area. Thus parathyroid adenoma was suspected.

Sestamibi Scans: Sestamibi scans of the neck showed no uptake and were found to be negative.

MRI Neck: MRI confirmed the findings of USG in the neck and parathyroid adenoma was found as hyperintense nodules on T2 scans.

Biopsy: Biopsy of the proximal left humerus was performed, and a brown spongy material consisting of several multinucleated giant cells without atypia was observed.

Case Presentation

A 20-year-old female presented to an outpatient clinic with pain and swelling around her left shoulder, persisting for six months. The swelling had progressively worsened over the past one and a half months. She had no family history of similar issues, no history of trauma, and no medical comorbidities.

Clinical Examination revealed swelling on left proximal humerus with tenderness on pressure. There was no warmth, redness, or neurovascular deficit observed around the shoulder.

Imaging:

- X-rays (Anteroposterior and Lateral Views) showed a well-defined lytic lesion with a cortical breach on the medial border of the proximal

CT Scan: CT scan showed multiple lesions in the body like humerus, sternum, D7 vertebrae, bilateral clavicle, bilateral scapula, multiple ribs, maxilla, mandible, radius, ulna and also sphenoid and temporal bones. Local part X-rays of all the parts were done to evaluate the lesions.

Treatment: After diagnostic work-up, the patient was referred to our Head and Neck department and underwent parathyroidectomy. Histopathology confirmed parathyroid adenoma. A shoulder arm pouch was provided for left shoulder pain. VAS scores decreased after surgery.

Results

Five out of our 6 patients were females. Also 4 out of our 6 patients were under the age of 25. 3 patients presented to us with multiple lytic lesions and other 3 patients had solitary lesions. One patient out of 6 presented to us with pathological fracture. Patients presented with extremity lesions. In the case described above, CT additionally demonstrated a lesion at the D7 vertebra. No neurological symptoms were present on clinical examination. Table 2 summarises pre- and postoperative laboratory values. Only 2 out of 6 patients had a positive sestamibi scan; USG and MRI of the neck showed parathyroid adenoma in all cases, confirmed by histopathology.



Figure 2. Case of a 45 year female with multiple lytic cystic lesions in the body:

A) X-ray of knee with leg showing well defined purely lytic lesion in shaft tibia.

B) X-ray of knee with femur of opposite side showing well defined lytic expansile lesion of distal femur.

C) X-ray of knee with femur after 3 months of parathyroidectomy showing reduction in cavity size, sclerosis and subperiosteal resorption.

Follow-up: The patient was monitored both clinically (through physical examination) and radiologically (with X-rays or other imaging and blood investigations). Follow-ups were conducted monthly for the first 3 months and afterwards every 3 months for up to 1 year. Follow up X-rays of all parts showed reduction in cavity size and significant sclerosis post operatively as a sign for healing.

Following parathyroidectomy, mean serum PTH and calcium levels decreased significantly (two-sided paired t-tests: $p = 0.0085$ and $p = 0.0293$, respectively). Changes in serum phosphorus and alkaline phosphatase were not statistically significant ($p = 0.3708$ and $p = 0.0903$, respectively). Mean VAS scores decreased from 67 to 24; statistical significance could not be assessed from the reported summary data. (Table 2).

Discussion

PHPT is the third most common endocrine disease after diabetes and thyroid disease. Its incidence ranges from 0.025% to 0.065%, with the highest incidence in postmenopausal women

practices become more common, the clinical presentation of PHPT becomes less severe (13).

Due to the high amount of patients presenting with lytic lesions, we made a common practice to

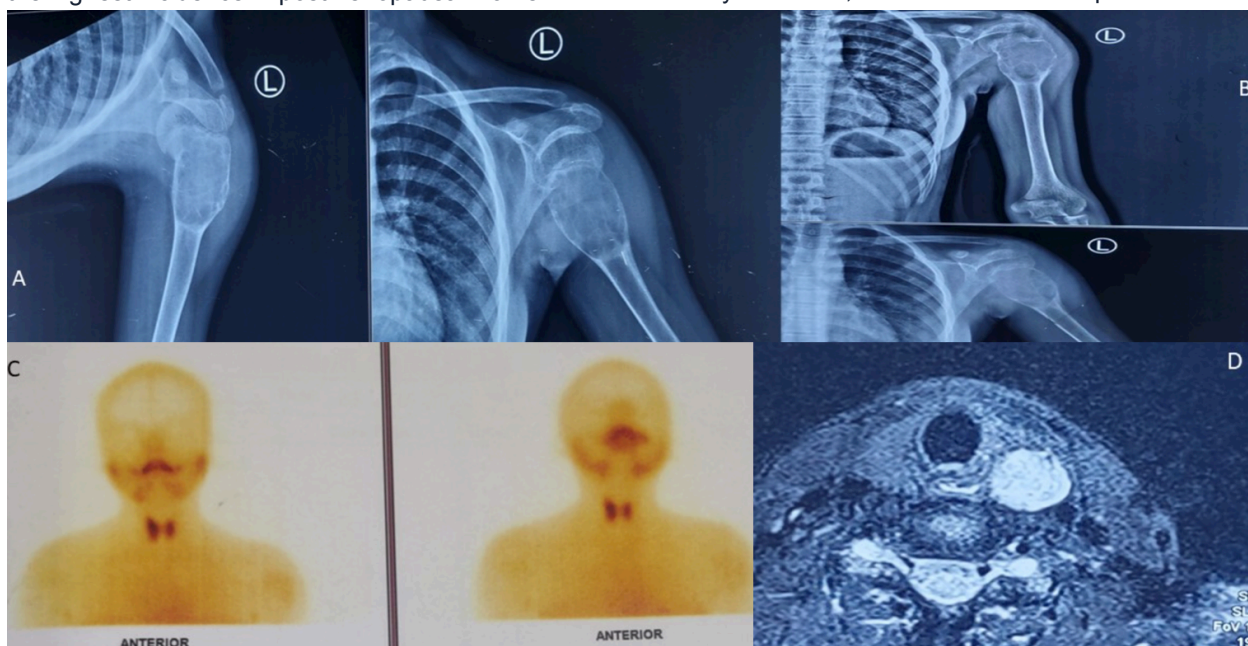


Figure 3. This a 12 year female with lytic expansile lesion in proximal humerus:

- A) X-ray of humerus with shoulder showing lytic lesion in proximal humerus.
- B) X-ray of humerus with shoulder after parathyroidectomy showing significant sclerosis.
- C) Technetium 99-m MIBI scan showing no evidence of tracer concentration in neck region.
- D) MRI Neck showing 8x8x12 mm well defined altered signal intensity lesion in postero-inferior to left lobe of thyroid gland showing parathyroid adenoma.

(7,8,9). The abnormally increased secretion of PTH usually affects calcium levels, phosphate levels, and bone metabolism. It usually causes renal and skeletal manifestations. However, due to the routine blood calcium and phosphorus tests, PHPT is generally detected in the early stage. Therefore, most patients with PHPT are asymptomatic (10).

Brown tumour, which is one of the pathognomonic signs of PHPT, is a focal, tumour-like bony lesion caused by osteoclastic turnover of bone. Although it is reported that musculoskeletal manifestations in patients with PHPT can reach 54.7%, the incidence rate of brown tumor ranges from 1.5 to 4.5% (11,12).

The relationship between overt bone disease and primary hyperparathyroidism (PHPT) in regions lacking routine biochemical screening remains uncertain. It is yet to be determined whether this is due to delayed detection of PHPT or, as equally plausible, a result of excessive parathyroid hormone (PTH) activity exacerbated by insufficient or marginal vitamin D and calcium intake. With regard to the use of routine biochemical screening, it has been shown that when such

have detailed blood investigations like serum calcium, serum phosphorus and alkaline phosphatase. Any derangement in the values of this investigations were then observed in detail with a wide array of radiological investigations to rule out Brown tumor. In this way we were able to diagnose 6 cases of Brown tumor. The histopathological presentation of Brown tumors closely resembles that of giant cell tumors. Without the aid of blood tests and radiological investigations, our pathologists would likely have misdiagnosed these lytic lesions as giant cell tumors.

Our pre-biopsy investigations provided the pathologist with insights into abnormal serum parathyroid hormone levels, identifying Brown tumor as the primary differential diagnosis. We successfully managed all these lytic lesions without any additional operative intervention, relying solely on parathyroidectomy and vitamin D3 supplementation as recommended by our endocrinologist.

All lesions slowly regressed and the patients were asymptomatic from a period of 30 days post operatively to 6 months. Brown tumor in extremities is a rare presentation or even misdiagnosed as a Giant Cell Tumour and is very rarely

No	AGE	SEX	SITE	BISPHOSPHONATES PRE OPERATIVE	SERUM PTH (pg/ml) PRE OP	POST OP	SERUM CALCIUM (mg/dl) PRE OP	POST OP	SERUM PHOSPHORUS (mg/dl) PRE OP	POST OP	SERUM ALKALIKNE PHOSPHATASE (U/l) PREOP	POST OP	HISTOPATHOLOGY OF PARATHYROIDECTOMY	SESTAMIBI SCAN	MRI NECK
1	20	F	1. proximal humerus (34mm x 34mm x 74mm) 2. sternum 3. D7 vertebrae 4. bilateral clavicle 5. bilateral scapula 6. ribs 7. maxilla 8. mandible 9. radius 10. ulna 11. sphenoid 12. temporal bone	3 x zoledronic acid monthly									parathyroid adenoma	negative	parathyroid adenoma
2	20	F	5th metacarpal head	2 x denosumab weekly	268	52	9.48	8.42	3.86	3.41	73.5	69	parathyroid adenoma	negative	parathyroid benign lesion
3	23	M	Proximal tibia pathological fracture (44mm x 33mm x 54 mm)	3 x zoledronic acid monthly	929	139	13.7	8.46	1.29	2.81	1499	605	parathyroid adenoma	negative	parathyroid adenoma
4	45	F	1. distal femur 2. tibia 3. mandible 4. pterygoid plate	3 x zoledronic acid monthly	731	20.9	11.6	9.68	2.31	3.98	220	88	parathyroid adenoma	parathyroid adenoma	parathyroid adenoma
5	12	F	Proximal humerus	none	206	74	10.3	9.99	5.1	4.63	275	101	parathyroid adenoma	negative	parathyroid adenoma
6	28	F	1. proximal tibia (58mm x 60mm x 90mm) 2. bilateral femur 3. bilateral humerus 4. bilateral clavicle 5. mandible 6. iliac bones 7. scapula 8. ribs 9. 2nd metacarpal	3 x zoledronic acid monthly	691	89.5	14.4	8.29	1.18	2.05	768	207	parathyroid adenoma	parathyroid adenoma	parathyroid adenoma

Table 1 Clinical and demographic features of patients affected with browns tumor

Measure	PTH (pg/mL)	Calcium (mg/dL)	Phosphorus (mg/dL)	Alkaline phosphatase (U/L)	VAS score
Mean pre-op	660	12.56	2.56	831.41	67
Mean post-op	87.9	8.85	2.98	530.33	24
p (two-sided)	0.0085	0.0293	0.3708	0.0903	Not assessed

Table 2. Mean values and two-sided paired t-tests (n = 6); unadjusted p-values.

No.	Author & Ref.	Year	Age	Gender	Localisation	Cases	Serum calcium (mmol/l) normal range 2.20-2.55	Serum phosphorus(mmol/l) normal range 0.81-1.45	Parathyroid hormone (pg/ml) normal range 15-65	Alkaline phosphatase (IU/l) normal range 35-104	sestamibi	Final histopathology	usg neck
1	Psaila 14	2020	35	Female	Maxilla, skull, scapula and	1	3.49	0.6	918	n.a.	positive	parathyroid adenom	positive
2	Ngo 15	2021	35	Female	Iliac bone and femur	1	3.57	0.51	1497	339	n.a.	parathyroid adenom	positive
3	Dhaniwala 16	2020	28	Female	Both femora and pelvis	1	2.69	n.a.	1632	1686	n.a.	parathyroid adenom	positive
4	Lenherr-Taube 17	2020	13	Male	Multifocal lesions through	1	3.85	0.68	980	1245	positive	parathyroid adenom	positive
5	Hu 18	2019	50	Female	Femur, humerus, spine	1	2.61	n.a.	1811	n.a.	n.a.	parathyroid adenom	n.a
6	Aslan 19	2018	14	Female	Tibia, femur	1	3.35	0.72	1441	636	positive	parathyroid adenom	positive
7	Goyal 20	2018	16	Female	Femur	1	1.98	0.9	840	1324	n.a.	n.a	n.a
8	Panagopoulos 21	2018	53	Male	Ulna, radius, tibia, metaca	1	3.63	0.74	1453	n.a.	positive	parathyroid adenom	positive
9	Garla 22	2018	50	Female	Knee, femur, iliac bone	1	3.08	n.a.	1810	n.a.	positive	parathyroid adenom	positive
10	Baig 23	2018	77	Female	Femur, ischium	1	2.8	n.a.	3842	n.a.	n.a.	n.a	n.a
11	Misorowski 24	2017	28	Male	Clavicle	4	3.3	0.48	1560	624	n.a.	n.a	n.a
			56	Female	Knee		3.45	0.68	336	356	n.a.	n.a	n.a
			58	Male	Humerus		3.55	0.58	458	459	n.a.	parathyroid cancer	n.a
			23	Male	Pubic bone		3.65	0.94	n.a.	1035	n.a.	ectopic parathyroid	n.a
12	Shekhawat 25	2017	31	Female	Metatarsal bone	1	2.8	0.65	2543	1049	positive	parathyroid adenom	positive
13	Vaishya 26	2017	25	Female	Tibia	1	2.25	1.39	495	450	n.a.	n.a	n.a
14	Jervis 27	2017	58	Female	Multiple osteolysis	1	2.65	2.01	400	341	positive	parathyroid adenom	positive
15	Schnyder 28	2017	72	Female	Os ilium and acetabulum	1	3.55	0.56	1466	189	n.a.	parathyroid adenom	positive
16	Park 29	2016	57	Female	Both femora	1	3.63	0.65	2720	2417	n.a.	parathyroid carcinoma	positive
17	Riestra Fernández 30	2017	58	Male	Both tibiae, ribs	1	3.85	0.9	1027	335	n.a.	n.a	n.a
18	Hussain 31	2016	21	Female	Mandible, maxilla, sternum	1	2.16	0.71	1653	875	positive	parathyroid adenom	positive
19	Sathyakumar 32	2016	28	Female	Pelvis, both femora	1	3.1	0.65	1900	1112	positive	parathyroid adenom	positive
20	Our study	2023	20	Female	proximal humerus	6	3.975	0.9	1133	2153	positive	parathyroid adenom	positive
			20	Female	5th metacarpal head		2.37	0.21	268	73.5	positive	parathyroid adenom	positive
			23	Male	Proximal tibia		3.425	0.07	929	1499	positive	parathyroid adenom	positive
			45	Female	distal femur		2.9	0.128	731	220	positive	parathyroid adenom	positive
			12	Female	Proximal humerus		2.575	0.283	206	275	positive	parathyroid adenom	positive
			28	Female	1. proximal tibia (58mm x 60mm x 90		3.6	0.065	691	768	positive	parathyroid adenom	positive

Table 3 Review of literature on Browns tumor of extremities

reported. We present a case series involving six patients diagnosed with brown tumors who were treated exclusively with parathyroidectomy.

We compared 19 other studies from 2016 to 2020 on Brown tumors of the extremities and this was the comprehensive review of literature (Table 3). To our knowledge this is the most comprehensive collection of Brown tumor of appendicular skeleton. The limitation of the current study was its

retrospective nature and small number of patients. Thus we suggest a multi-center study with a larger number of patients in future studies.

Conclusion

When radiographic evidence of a lytic lesion and hypercalcemia are present, Brown tumor should always be considered in the differential diagnosis. Brown tumor has distinctive imaging appearance

and with solid components were intermediate to low intensity on T1- and T2-weighted images, while the cystic components were hyperintense on T2-weighted images and showed fluid-fluid levels. MRI of the neck confirms the findings of USG of the neck and parathyroid adenoma were found as hyperintense nodes on T2-weighted images. Parathyroidectomy has excellent results allowing us to manage lytic lesions conservatively.

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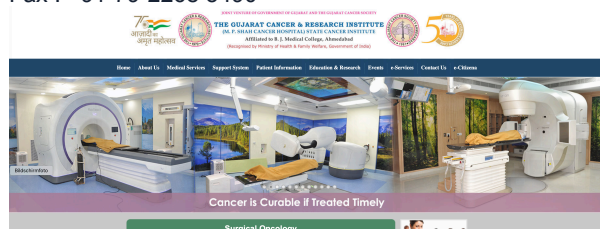
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