Telangiectatic osteosarcoma arising in osteogenesis imperfecta

Ferreira DG[1], Spranger A[1], Almeida P[1], Presa D[2], Fernandes I[3], Soares do Brito J[1]

ACTA REUMATOL PORT. 2021;46:171-176

ABSTRACT

We present the case of a 32-year-old man with a diagnosis of type-III osteogenesis imperfecta who developed a telangiectatic osteosarcoma in the proximal right tibia. An above-knee amputation was performed and after one-year follow-up, pulmonary metastatic lesions were detected on the thoracic CT scan. Palliative chemotherapy was proposed and to date the patient is still living and is under medical treatment.

The association between osteogenesis imperfecta and osteosarcoma is rare. There are only ten confirmed reports of this unusual situation, but to our knowledge this is the first case reported with a telangiectatic osteosarcoma arising in this particular setting.

Keywords: Telangiectatic osteosarcoma; Osteogenesis imperfect; Diagnosis; Management; Outcomes.

INTRODUCTION

Despite the common belief in the general medical community of an association between osteogenesis imperfecta (OI) and osteosarcoma (OS), this is a rare finding. In fact, to date there are only ten proven cases published in the English literature[1]. Both conditions are extremely rare and for that reason it is difficult to document a real association between the two diseases[2-5]. Nonetheless, most authors agree that the likelihood of an osteosarcoma developing in patients with OI is probably no greater than that found for the general population[6]. Meanwhile, for those rare patients with an osteosarcoma arising in osteogenesis imperfecta, a classic delay in diagnosis is usually described, mainly due to two major factors: the difficulty in differentiating an hyperplastic callus from an osteogenic tumor on plain x-rays, and symptoms that can be very similar and non-characteristic[1]. These issues make proper management and good outcomes even more difficult.

Herein, the authors present a case of an OS arising in type III OI, more specifically, a case of telangiectatic osteosarcoma (TO). To our knowledge, this is the first case of this OS subtype to be found in the setting of OI.

CASE PRESENTATION

This is the case of a 32-year-old male patient who was born with full-term and normal delivery, however, with growth characterized by short stature, frontal bossing, and thoracic and limb dysmorphism. These features, associated with multiple non-traumatic fractures, were eventually responsible for the patient's total dependence. A diagnosis of type-III OI was made after medical investigation. There was no family history of this disease. This patient had initial follow-up care in a pediatric hospital, but he was lost to regular follow-up in adulthood.

In November 2018, the patient started to have pain, tenderness and progressive swelling in his proximal right leg. There was no previous history of any traumatic injury. Due to the persistence of symptoms for a month, the patient sought medical attention at his regional hospital. After plain X-rays and magnetic resonance imaging (MRI), an orthopedic surgeon requested referral to our hospital.

At our institution the examination identified an increased volume in the patient's right upper leg, associated with pain on palpation and a visible neovascularization (Fig.1). The plain X-rays (Figure 1) showed a neoformative process around the knee, the origin of which was probably at the proximal tibia. These findings were consistent with malignant bone tumor be-

1. Serviço de Ortopedia e Traumatologia, Centro Hospitalar Lisboa Norte, EPE; Hospital de Santa Maria
2. Serviço de Anatomia Patológica, Centro Hospitalar Lisboa Norte, EPE; Hospital de Santa Maria
3. Serviço de Oncologia Médica, Centro Hospitalar Lisboa Norte, EPE; Hospital de Santa Maria

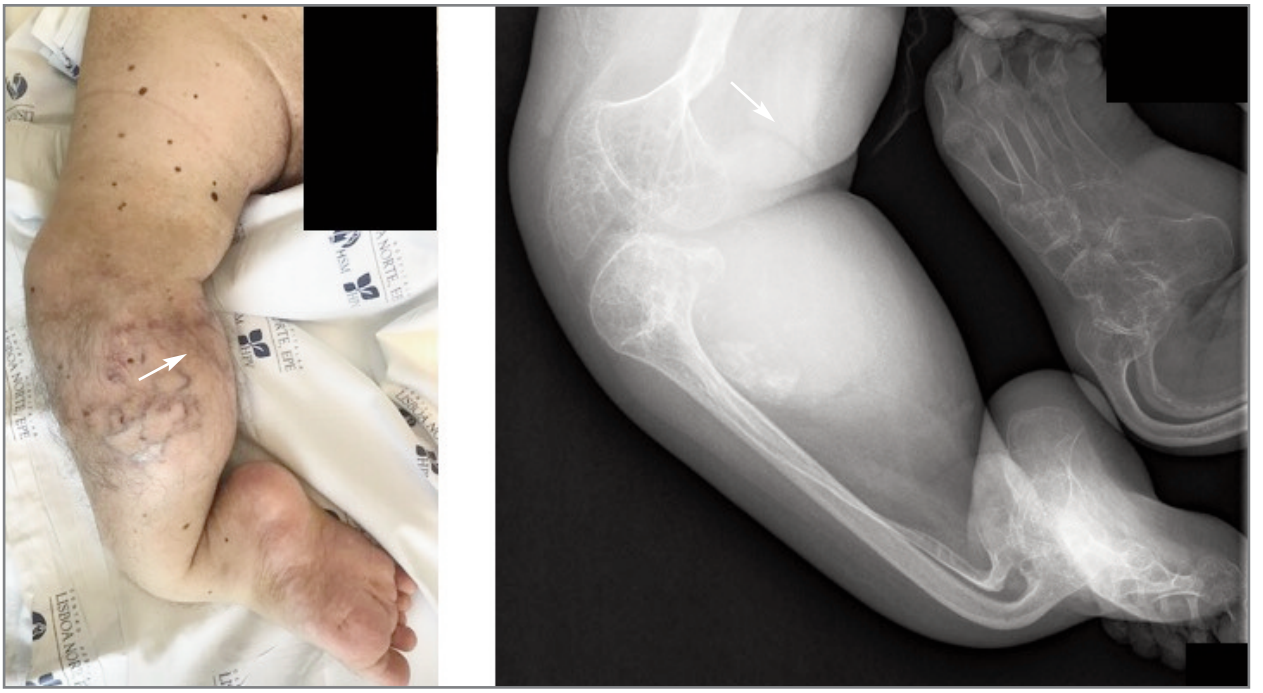

FIGURE 1. Left - Clinical photography showing a dysmorphic limb with increased volume and visible vascularization associated with a tumor/lesion in the right upper leg. Right - Plain X-ray showing severely dysmorphic bone structure and a neoformative process of the proximal right tibia.

havior and further studies were requested. The studies performed included thoracic, abdominal and pelvic staging via computed tomography (CT scan), bone scintigraphy, and biopsy of the lesion. The CT scan and bone scintigraphy showed no signs of multifocal disease, and the MRI revealed features of fluid-fluid levels, suggesting the possibility of telangiectatic osteosarcoma, an aneurismal bone cyst, or the event of a bony giant-cell tumor (Figure 2). The biopsy identified a hyalinized stroma with foci of calcification and scattered cells, with hyperchromatic and pleomorphic nuclei. The histological aspects were suggestive of malignancy, namely a bone malignancy such as osteosarcoma (Figure 3). Neoadjuvant chemotherapy before surgery was proposed, however this was refused by the patient. Nonetheless, the proposal for surgical above-knee amputation was accepted to better control the pain generated by the tumor.

The specimen in pathology confirmed the osteosarcoma diagnosis, namely a telangiectatic osteosarcoma (Figure 4). There were no complications with the stump and the patient was indicated for follow-up every three-months. Unfortunately, one year after surgery, metastatic lesions were detected in the

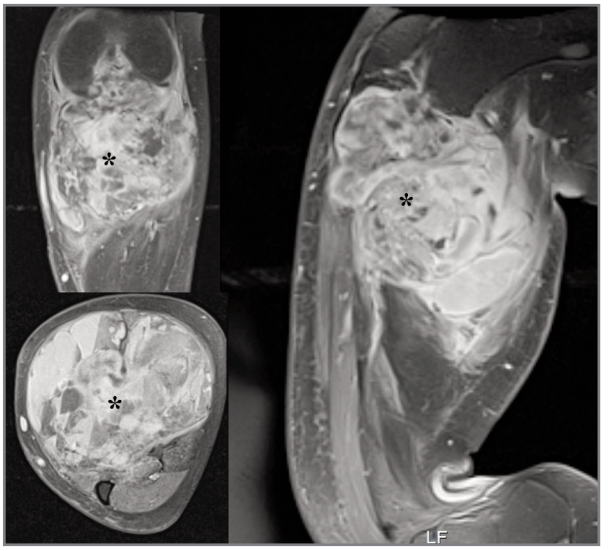

FIGURE 2. Upper left - T1-weight coronal imaging showing an agressive bone neoplasm arising from the proximal tibia. Lower left - T1-weight axial imaging showing the agressive bone neoplasm with fluid-fluid levels with visible septae. Right - T1-weight sagittal imaging showing the same agressive bone neoplasm arising from the proximal tibia.

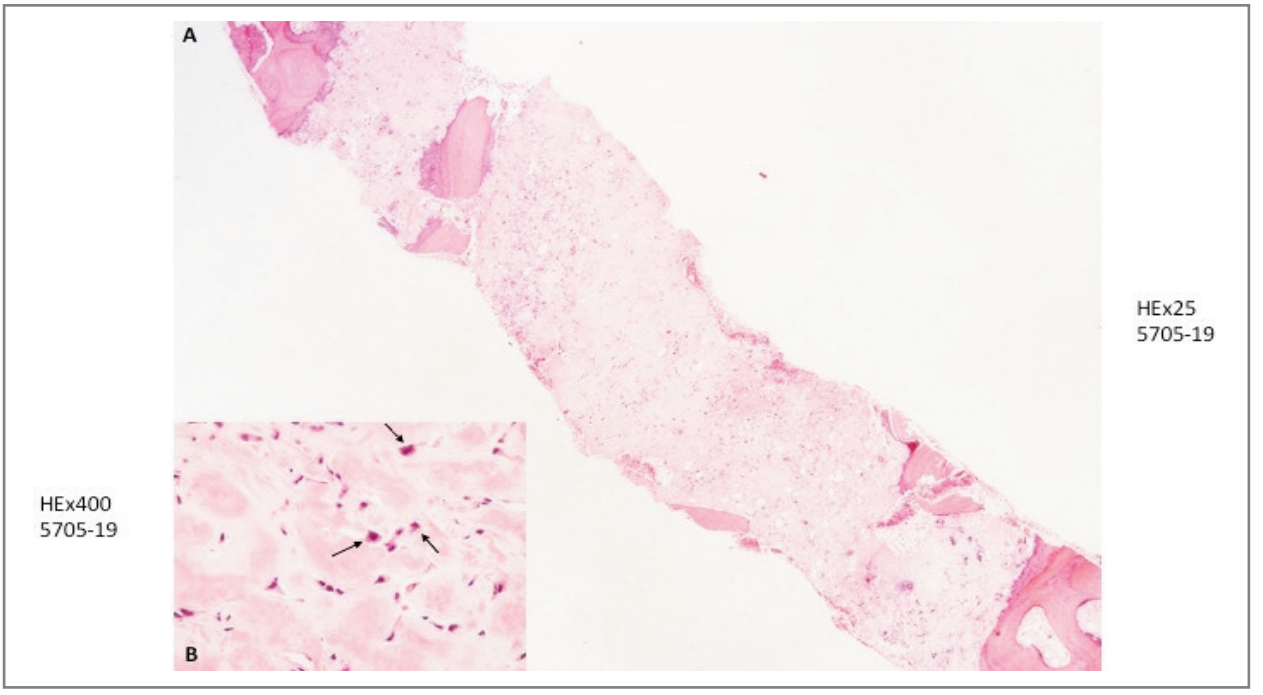

FIGURE 3. Biopsy of the proximal tibia neoplasm showing atypical poligonal cells and sclerotic stroma (A – 25X amplification; B – 400X amplification)

thoracic CT scan (Figure 5). At that point, palliative chemotherapy was proposed, which the patient accepted. Currently the patient is still living and is under medical treatment.

DISCUSSION

Osteogenesis imperfecta is a genetic disorder that increases bone fragility with an associated decrease in bone mass. Classically, four types of OI have been identified to simplify the prognosis for the different courses of the disease[7]. Type III OI is the most severe form in children who survive the neonatal period. It is characterized by very short stature, severe limb deformities, and scoliosis due to multiple fractures of the appendicular and axial skeleton. This group also has a typical triangular face and imperfect dentinogenesis[2-3, 8].

Both OI and OS are relatively rare with most authors understanding that OS in the setting of OI constitutes two rare and unrelated events[1]. In English literature, we can find a total of ten reported cases with concomitant diagnosis of OI and OS (Table I). To our knowledge, none of the patients involved in these cases were diagnosed with telangiectatic osteosarcoma, which is a rare high-grade malignant neoplasm accounting for less than 4% of all cases of OS[16]. This non-conventional subtype of OS usually occurs in the first and second decades of life[17]. Clinically, there is no difference in the presentation between telangiectatic and conventional osteosarcoma. The most common symptoms are local pain (especially during the night), tenderness, and the presence of a soft tissue mass[18]. The most common anatomic sites for telangiectatic osteosarcoma are the distal femoral metaphysis (42%) and proximal tibia (17%), which was the case for our patient[16].

A crucial aspect of evaluating an OS arising in the setting of OI is the diagnostic challenge. In fact, during the course of OI, as stated by Takahashi *et al*, there may be difficulty interpreting old and new radiographic changes due to the distorted bony morphology resulting from disease progression and recurrent fractures. Additionally, the plethora of symptoms of OI and its complications can be very similar to those of OS in its early stages[1]. Unlike most cases reported in the literature regarding conventional OS in the setting of OI, where diagnostic difficulties are systematically present, our case was not affected by this phenomena[1]. In fact, the different radiologic and histopathologic features of

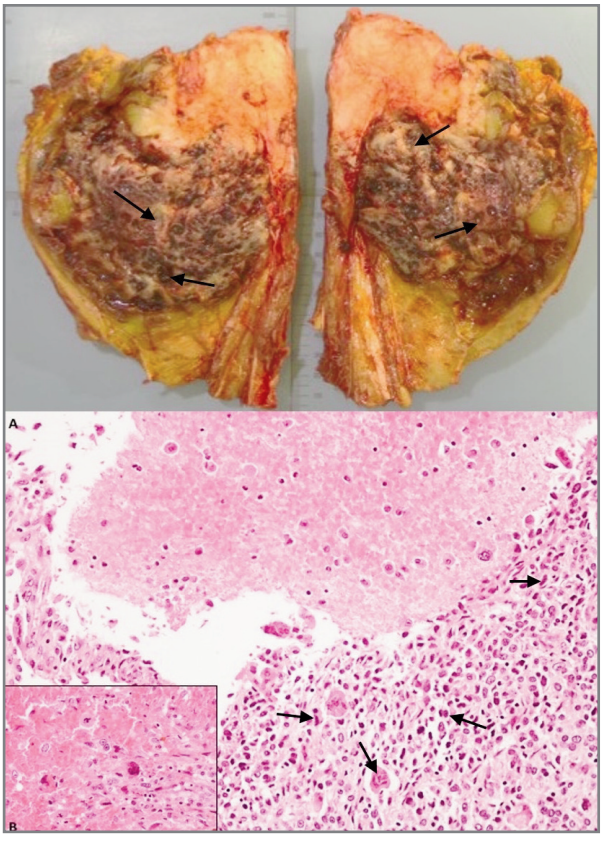

FIGURE 4. On top – Proximal tibia tumor in section: it is possible to observe the haemorragic aspect of the tumor and the typical cystic cavities seen in telangiectatic osteosarcomas; on bottom – Microscopy image showing mononuclear ovoid and fusiform cells, some disperse multinuclear cells and atypical cells in the cavities filled with blood (A – 200X amplification; B – 400X amplification)

telangiectatic osteosarcoma facilitated a distinction from the cases of conventional OS or hyperplastic callus formation that were found related to OI. On the other hand, other challenges were raised by the findings during clinical investigation, such as the need to differentiate a telangiectatic osteosarcoma from other entities like an aneurysmal bone cyst (ABC) or a giant-cell tumor (GCT), in order to facilitate adequate and prompt management[16,17,19,20]. However, the evidence of a tumor with clinically malignant behavior, the presence of a radiographically destructive and osteolytic neoplasm with little or no matrix mineralization, an MRI showing fluid-fluid levels with septae, and a bone scan with an intense uptake, made us suspect a telangiectatic osteosarcoma. Eventually, this suspicion was confirmed by the biopsy and final specimen histologic analysis[17,19].

Several studies in the literature concluded a similar prognosis for telangiectatic osteosarcoma and conventional osteogenic OS[21-23]. The advent of neoadjuvant chemotherapy greatly improved the prognosis for all these patients[24,25], but surgery still have a decisive role. Despite limb salvage and reconstructive surgery as the current gold standard for any given limb with OS, our particular patient had severe dysmorphism which made limb salvage impossible. An above-knee amputation was performed instead, and despite a specimen with clear margins, metastatic disease was found one year after surgery, which was not a surprise in the absence of chemotherapy.

The data collected in Table 1 regarding age, gender

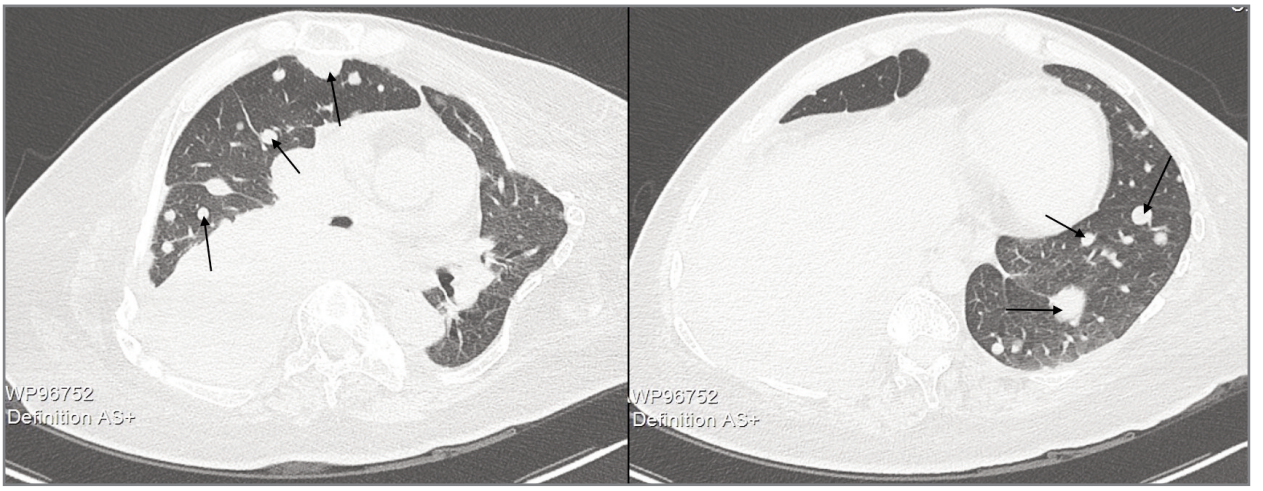

FIGURE 5. Left - One year post-operative thoracic CT scan showing metastatic lesions affecting the right lung. Right - One year post-operative thoracic CT scan showing severe metastatic lesions affecting the left lung

TABLE I. CASES REPORTED IN THE LITERATURE OF OSTEOSARCOMA IN THE SETTING OF OSTEOGENESIS IMPERFECTA

Year	Reference first author	Patient's age	Gender	OS subtype *(extrapolated from imaging and histologic findings)	Location	Treatment	Survival
1940	Jewell FC9	49	Male	Conventional osteosarcoma*	Pelvis	Amputation	<1 year
1967	Klenerman L10	8	Female	Conventional osteosarcoma*	Femur	Palliative	6 months
		13	Female	Conventional osteosarcoma*	Femur	Disarticulation	3 years
1978	Lasson U11	13	Male	Conventional osteosarcoma*	Femur	Amputation	>6 months
1979	Reid BS12	14	Male	Conventional osteosarcoma*	Femur	Amputation	10 months
1979	Rutkowski R13	15	Male	Conventional osteosarcoma*	Femur	Hip disarticulation	8 months
1995	Gagliardi JA6	21	Female	Conventional osteosarcoma*	Femur	Hemipelvectomy	Unknown
1999	Bedi HS14	37	Female	Conventional osteosarcoma*	Scapula	Forequarter amputation	4 months
2002	Maiya S15	6	Male	Conventional osteosarcoma	Femur	Distal femur endoprothesis and total femur later on	>6 years
2004	Takahashi S1	24	Male	Conventional osteosarcoma*	Femur	Amputation	>2 years
2020	Ferreira D	32	Male	Telangiectatic osteosarcoma	Tibia	Amputation	>1 year

and location of OS in patients with OI, presented no significant differences when compared with the general population. In fact, there is a predominance of males in the first two decades of life, and osteosarcomas arrising in the long bone metaphysis of lower limbs[5]. Regarding the treatment modality and oncologic outcomes obtained in the population described in table 1, proper comparison with general population is not possible, since at least half of the reports are previous to the introduction of chemotherapy and multimodal therapies, which represented the leap forward in osteosarcoma treatment. Additionally, demographic data, histologic findings, the presence of metastases and the response to chemotherapy are the greatest predictors of survival, which are not related to the OI diagnosis.

The clinical case presented above illustrates the need for awareness of this rare event: OS arising in the setting of OI. Furthermore, we believe we describe the first case of telangiectatic osteosarcoma arising with the diagnosis of OI. This information gives practitioners additional knowledge to better understand this uncommon association.

CORRESPONDENCE TO
Joaquim Soares do Brito
Serviço de Ortopedia e Traumatologia
Centro Hospitalar Lisboa Norte, EPE
Hospital de Santa Maria, Avenida Professor Egas Moniz
E-mail: joaquimsoaresdobrito@gmail.com

REFERENCES

1. Takahashi S, Okada K, Nagasawa H, Shimada Y, Sakamoto H and Itoi E. Osteosarcoma occurring in osteogenesis imperfecta. Virchows Archiv: an International Journal of Pathology. 2004 May;444(5):454-458. DOI: 10.1007/s00428-004-0985-5.
2. Forlino A, Marini, JC. Osteogenesis imperfecta. Lancet, 2016; 387(10028): 1657-1671. DOI: 10.1016/S0140-6736(15) 00728-X.
3. Marini JC. Osteogenesis imperfecta: comprehensive management. Advances in pediatrics, 1988; 35: 391-426. PMID: 3055864.
4. Ries LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL et al. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995, National Cancer Institute, SEER Program. NIH Pub. No.99-4649. Bethesda, MD, 1999.
5. Mirabello L, Troisi R, Savage S. Osteosarcoma Incidence and Survival Rates from 1973 to 2004. Data From the Surveillance, Epidemiology, and End Results Program. Cancer, 2009; 115. 1531-43. 10.1002/cncr.24121.
6. Gagliardi JA, Evans EM, Chandnani VP, Myers JB, Pacheco CM. Osteogenesis imperfecta complicated by osteosarcoma. Skeletal Radiology, 1995; 24.4:308-310. DOI: 1 0.1007/BF00198423
7. Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 1979; 16: 101–16. DOI: 10.1136/jmg.16.2.101.

8. Marini JC, Forlino A, Bächinger HP, Bishop NJ, Byers PH, Paepe AD, et al. Osteogenesis imperfecta. Nature Reviews Disease Primers, 2017;3:17052. DOI: 10.1038/nrdp.2017.52.
9. Jewell F, Lofstrom J. Osteogenic Sarcoma Occurring in Fragilitas Ossium. Radiology, 1940;34(6):741–743. DOI: 10.1148/34.6.741.
10. Klenerman L, Ockenden BG, Townsend AC. Osteosarcoma occurring in osteogenesis imperfecta. Report of two cases. J Bone Joint Surg, 1967;49:314–323. PMID: 5229569.
11. Lasson U, Harms D, Wiedemann H. Osteogenic sarcoma complicating osteogenesis imperfecta tarda. Eur J Pediatr, 1978;129:215–218. DOI: 10.1007/BF00442166
12. Reid BS, Hubbard JD. Osteosarcoma arising in osteogenesis imperfecta. Pediatr Radiol, 1979;8:110–112. DOI: 10.1007/BF00974002
13. Rutkowski R, Resnick P, McMaster JH. Osteosarcoma occurring in osteogenesis imperfecta. A case report. J Bone Joint Surg, 1979;61:606–608. PMID: 285932.
14. Bedi HS, Kaufman DV, Choong PF, Slavin JL. Osteosarcoma of the scapula arising in osteogenesis imperfecta. Pathology, 1999;31:52–54. DOI: 10.1080/003130299105557.
15. Maiya S, Grimer RJ, Ramaswamy R, Deshmukh NS. Osteosarcoma occurring in osteogenesis imperfecta tarda. Int Orthop. 2002;26(2):126-128. DOI:10.1007/s00264-001-0323-3.
16. Sangle NA, Layfield LJ. Telangiectatic osteosarcoma. Arch. Pathol. Lab. Med. 2012 May;136(5):572-6. DOI: 10.5858/arpa.2011-0204-RS.
17. Yarmish G, Klein M.J, Landa J, Lefkowitz RA, Hwang S. Imaging Characteristics of Primary Osteosarcoma: Nonconventional Subtypes. RadioGraphics, 2010; 30(6);1653–1672. DOI: 10.1148/rg.306105524.
18. Papagelopoulos PJ, Mavrogenis AF, Savvidou OD, Benetos IS, Alanis EC, Soucacos PN. Pathological fractures in primary bone sarcomas. Injury. 2008; 39(4):395-403. DOI: https://doi.org/10.1016/j.injury.2007.07.018
19. Liu JJ, Liu S, Wang JG, Zhu W, Hua YQ, Sun W, et al. Telangiectatic osteosarcoma: a review of literature. Onco Targets Ther. 2013; 6:593-602. DOI: 10.2147/OTT.S41351.
20. Klein, MJ, Siegal GP. Osteosarcoma. American Journal of Clinical Pathology. 2006; 125(4):555–581. DOI: 10.1309/UC6KQHLD9LV2KENN.
21. Matsuno T, Unni KK, McLeod RA, Dahlin DC. Telangiectatic osteogenic sarcoma. Cancer. 1976; 38(6):2538–2547. DOI: https://doi.org/10.1002/1097-0142(197612)38:6%3C2538::AID-CNCR2820380643%3E3.0.CO;2-1.
22. Mervak TR, Unni KK, Pritchard DJ, McLeod RA. Telangiectatic osteosarcoma. Clin Orthop Relat Res. 1991; 270:135–139. PMID: 1884532.
23. Farr GH, Huvos AG, Marcove RC, Higinbotham NL, Foote FW Jr. Telangiectatic osteogenic sarcoma. A review of twenty-eight cases. Cancer. 1974; 34(4):1150–1158. DOI: https://doi.org/10.1002/1097-0142(197410)34:4<1150::AID-CNCR2820340426>3.0.CO;2-S.
24. Rosen G, Huvos AG, Marcove R, Nirenberg A. Telangiectatic osteogenic sarcoma. Improved survival with combination chemotherapy. Clin Orthop Relat Res. 1986; 207:164–173. PMID: 2424660.
25. Weiss A, Khoury JD, Hoffer FA, Wu J. Telangiectatic osteosarcoma: the St Jude Children's Research Hospital's experience. Cancer. 2007;109(8):1627–1637. DOI: 10.1002/cncr.22574