Fibrous dysplasia (FD), with possible GNAS (guanine nucleotide-binding protein/a-subunit)-I gene mutations, is typically a benign fibro-osseous lesion that chiefly affects maxillofacial area causing facial deformity. Sarcomatous change of FD is rare and the frequency of sarcomatous transformation differs from less than 1% (monostotic/polystotic cases) to 4% (McCune-Albright/Jaffe-Lichtenstein syndrome). Osteosarcoma is the major histologic type of malignant transformation of FD, followed by fibrosarcoma, chondrosarcoma, and malignant fibrous histiocytoma, with most cases reported years after radiation treatments. Here, we reported an osteosarcoma spontaneous occurring in a Taiwanese patient with maxilla FD without prior radiotherapy with pertinent literature review.

A 65-year-old female patient complained a sudden painful ulcerated swelling over the left palate for 12 months. A long-standing stabilized FD over the left maxilla was diagnosed in another hospital with neither surgical nor radiation treatment before. Extraoral examination revealed a bony swelling over the left maxilla. Panoramic radiography showed an ill-defined mixed radiolucent and radiopaque lesion over the left upper edentulous area up to the left maxillary sinus. 3D-cone beam computed tomography (CBCT) revealed extensive bony swelling over left maxilla. Reformatted CBCT images showed full occupation of the left maxillary sinus by a mixed radiolucent-radiopaque destructive mass extending below the infraorbital area. No alteration of eyesight was complained. Increased level of serum alkaline phosphatase was noted. A bony malignancy associated with pre-existing FD was considered. Incisional biopsy revealed a high-grade osteosarcoma characterized with osteoid tissues showing highly pleomorphic cells with bizarre nuclei. Subsequently, radical resection was performed. Histopathological examination of the surgical specimen showed bizarre osteoid tissues adjacent to and infiltrated into areas featured with FD with irregular-shaped trabeculae of woven bone within fibrous stroma. A high-grade osteosarcoma arising from pre-existing maxilla FD has been rendered. GNAS-I mutations of the malignant tissues revealed negative result. The patient died of tumor after 11-month follow-up. Reviewing English literature, to our knowledge, 15 spontaneous osteosarcoma cases in pre-existing non-syndromic maxillofacial FD without previous irradiation are identified for the recent ten years (2010-2019); the clinical features (together with the current case) are summarized in Table 1. Briefly, the male-to-female ratio was 1:1.67 and the age of the patients ranged from 8 to 65 years with the mean age of 42.7 years. The present case is the oldest of such disease and is the first case in Taiwan. The majority of patients were belonged to the 6th decade (five cases) as high as 14 cases reported from Asian countries (China, 11 cases; one case each from Taiwan (our case), Korea, and Irian); the remaining two cases documented each from UK and USA. There were ten polyostotic cases with only six cases including our case) of monostotic form. The time-interval between initial FD and later malignant change was available for nine cases.

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with the mean duration being 30 years (range: 8–50 years); two cases (including our case), despite without exact duration, were judged as long-standing FD according to the given case history, whereas the remaining five cases were diagnosed simultaneously implicating that the delayed detection of FD, which was noted until the occurrence of malignant transformation. Most common clinical presentations included rapid-increased/sudden swelling (all cases including our case), pain (6 cases including our case), local numbness (6 cases), and intraoral ulceration (4 cases including our case). Eyesight problem was noted in two cases. Osteosarcoma predominantly involved the left maxilla (10 cases including our case), followed by the left mandible (4 cases) and the right mandible (2 cases). All (including our case) but one patient receiving radical resection with/without chemotherapy and/or radiotherapy. Fourteen patients including our case had available follow-up data indicating very poor prognosis with only 3 alive and 11 patients including our case died of disease during the follow-up period (several-week–101-month).

The genetic etiology of FD is well-documented being resulted from two-point mutation in GNAS-I protein; however, such mutations do not contribute to the malignant change of FD. The lack of GNAS-I mutation in the current case is concurred to the findings of Pollandt et al. who demonstrated constant absence of the GNAS-I mutation in an osteosarcomatous variant of FD, indicating a different genetic etiology for malignant change of FD. Additionally, albeit rare, spontaneous malignant transformation of FD without prior radiotherapy is well-confirmed; hence, dental practitioners should aware the happening of spontaneous sarcomatous change, particularly osteosarcoma, when FD patients presented with above-mentioned symptoms and radiological features of malignancy.

Figure 1 Clinical, radiographic, and microscopic pictures of the current case of spontaneous osteosarcoma arising from pre-existing fibrous dysplasia (FD) without prior irradiation. (A) Ulcerated swelling over the left palate. (B) Facial asymmetry with bony swelling over the left maxilla. (C) Panoramic radiography: an ill-defined mixed radiolucent-radiopaque expansion extending from the upper-left edentulous area to maxillary sinus. (D) 3D-cone beam computed tomography (CBCT) revealed an extensive bony swelling over the left maxilla. (E) Reformatted axial, coronal, and sagittal CBCT images showed total occupation of the left maxillary sinus by a mixed radiolucent-radiopaque destructive mass. (F) Incisional biopsy: high-grade osteosarcoma characterized with malignant osteoid tissues showing highly pleomorphic cells with bizarre nuclei (hematoxylin and eosin stain, H&E; magnification, 200 ×). (G, H) Surgical specimen upon radical resection: oral (G) and frontal (H) view. (I–K) Histopathological examination of surgical specimens: sarcomatous (*) and FD (●) areas (H&E; magnification, 4 ×) (I); bizarre osteoid tissues (left portion) adjacent to area featured with FD with irregular-shaped trabeculae of woven bone within fibrous stroma (right portion) (H&E; magnification, 100 ×) (J); tumor cells within sarcomatous area showing highly cellular atypia with numerous abnormal mitoses (H&E; magnification, 100 ×) (K).
| Authors (year) | Country | Age, years | Gender | Primary site of malignancy | Type of FD | Duration of FD, years | Symptoms of malignancy | Treatment of malignancy | Follow-up |
|---------------|---------|------------|--------|-----------------------------|-----------|----------------------|------------------------|------------------------|-----------|
| Kim et al. (2010) | Korea | 50 | Female | Right mandible | Monostotic | 25 | Swelling, 1 month | Neoadjuvant chemotherapy, radical resection, postoperative adjuvant chemotherapy | 24 months, alive, no evidence of disease |
| Varghese et al. (2010) | UK | 47 | Male | Left maxilla | Monostotic | Not available | Pain, rapid enlarged swelling, intraoral ulceration; 1.5 month | Frozen section, palliative radiotherapy | A few weeks, died of tumor |
| Sadeghi et al. (2011) | Iran | 16 | Male | Left maxilla | Monostotic | 0 | Rapid swelling, diplopia, 4 months | Radical resection; CCRT | 18 months, died of tumor |
| Cheng et al. (2013) | China | 55 | Male | Left maxilla | Polyostotic | 45 | Pain, local numbness, trismus | Incisional biopsy | 6 months, died of tumor |
| Cheng et al. (2013) | China | 57 | Female | Left maxilla | Polyostotic | 43 | Facial swelling, intraoral ulceration, bleeding | Radical resection | 23 months, alive, no evidence of disease |
| Cheng et al. (2013) | China | 26 | Female | Left maxilla | Polyostotic | 20 | Accelerated growth, local numbness, pain | Radical resection & postoperative radiotherapy | 16 months, died of tumor |
| Sun et al. (2014) | China | 55 | Male | Left mandible | Polyostotic | 50 | Swelling, pain, local numbness; 1 month | Radical resection | 44 months, died of tumor |
| Sun et al. (2014) | China | 55 | Male | Left maxilla | Polyostotic | 38 | Swelling, intraoral ulceration; 2 months | Radical resection | 57 months, died of tumor |
| Sun et al. (2014) | China | 31 | Female | Left mandible | Polyostotic | 8 | Swelling, local numbness; 0.5 month | Radical resection | 15 months, alive with lung metastasis |
| Sun et al. (2014) | China | 28 | Female | Left maxilla | Polyostotic | 20 | Swelling, local numbness, headache; 6 months | Radical resection, radiotherapy | 62 months, died of tumor |
| Sun et al. (2014) | China | 41 | Female | Left maxilla | Polyostotic | 0 | Swelling, pain, decreased visual acuity; 1 month | Radical resection, radiotherapy | 57 months, died of tumor |
| Sun et al. (2014) | China | 26 | Female | Left maxilla | Polyostotic | 0 | Swelling, local numbness; 0.5 month | Radical resection | 77 months, died of tumor |
| Sun et al. (2014) | China | 41 | Female | Right mandible | Monostotic | 0 | Swelling; 2 months | Radical resection | 101 months, died of tumor |
| Sun et al. (2014) | China | 8 | Male | Left mandible | Polyostotic | 0 | Swelling; 2 months | Incisional biopsy | Unknown, lost to follow-up |
| Pack et al. (2016) | USA | 39 | Female | Left mandible | Monostotic | 21 | Swelling, pain, paresthesia | Radical resection | Not available |
| Su et al. (present case) | Taiwan | 65 | Female | Left maxilla | Monostotic | Not available | Swelling, pain, intraoral ulceration, 12 months | Radical resection | 11 months, died of tumor |

*a* Duration between initial presentation of FD and later osteosarcoma occurrence.

*b* Long-standing FD but the exact duration has not been given.
Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jds.2019.04.002.

References

1. Tabareau-Delalande F, Collin C, Gomez-Brouchet A, et al. Diagnostic value of investigating GNAS mutations in fibrous dysplasia and 40 other fibro-osseous lesions: a retrospective study of 91 cases of fibrous dysplasia. Mod Pathol 2013;26:911–21.
2. Schwartz DT, Alpert M. The malignant transformation of fibrous dysplasia. Am J Med Sci 1964;247:1–20.
3. Sun TT, Tao XF, Shi HM. Spontaneous osteosarcoma in cranio-maxillofacial fibrous dysplasia: clinical and computed tomographic features in 8 cases. Oral Surg Oral Med Oral Pathol Oral Radiol 2014;118:e24–31.
4. Kim GT, Lee JK, Choi BJ, Kim J, Han SH, Kwon YD. Malignant transformation of monostotic fibrous dysplasia in the mandible. J Craniofac Surg 2010;21:601–3.
5. Varghese AI, Harrop CW, Smith WP. Malignant transformation of fibrous dysplasia of the maxilla. Int J Clin Pract 2010;64:121–2.
6. Sadeghi SM, Hosseini SN. Spontaneous conversion of fibrous dysplasia into osteosarcoma. J Craniofac Surg 2011;22:959–61.
7. Cheng J1, Yu H, Wang D, et al. Spontaneous malignant transformation in cranio-maxillofacial fibrous dysplasia. J Craniofac Surg 2013;24:141–5.
8. Pack SE, Al Share AA, Quereshy FA, Baur DA. Osteosarcoma of the mandible arising in fibrous dysplasia-A case report. J Oral Maxillofac Surg 2016;74:2229. e1–e4.
9. Pollandt K, Engels C, Kaiser E, Werner M, Delling G. Gsalpha gene mutations in monostotic fibrous dysplasia of bone and fibrous dysplasia-like low-grade central osteosarcoma. Virchows Arch 2001;439:170–5.

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