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Juvenile ossifying fibroma accompanied with low-grade central osteosarcoma in sinonasal: a rare case report

Muchamad Ridotu Solichin[1], Fikar Arsyad Hakim[2]*, Ery Kus Dwianingsih[1]

[1]Department of Anatomical Pathology, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia, [2]Department of Anatomical Pathology, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia

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ABSTRACT

Sinonasal osteosarcoma is comparatively rare and accounts for 6.5% of all osteosarcomas. The five-year survival rate is less than 25% and may be improved to 60% when chemotherapy is initiated earlier. The diagnosis of low-grade central osteosarcoma requires a meticulous histopathological examination because histopathologically the tumor may mimic fibro-osseus neoplasm. We report a 12 y.o. male patient who complained of a lump on the face for 4 yr with symptoms of nasal discharge, congestion, epistaxis, and a feeling of fullness in the ears. Sinonasal biopsy was later performed and revealed an inverted papilloma. Two months after the biopsy procedure, mass extirpation and medial maxillectomy were performed. Histopathology examination confirms the diagnosis of ossifying fibroma accompanied by low-grade central osteosarcoma. Low-grade central osteosarcoma is an exceptionally rare variant, and the diagnosis is occasionally difficult. It can be misdiagnosed as a benign lesion, especially fibrous dysplasia or ossifying fibroma. Histomorphological, the discovery of atypical tumor cells producing osteoid matrix can be used to confirm that the lesion is a malignant lesion of low-grade central osteosarcoma. As demonstrated in our case, the tumor can consist of a trabecular and curvilinear arrangement of immature bone, at the edges of which there is an osteoblastic rimming appearance with a background of connective tissue stroma which is a histopathological feature of ossifying fibroma.

ABSTRAK

Osteosarkoma sinonasal relatif jarang terjadi dan berkontribusi sekitar 6,5% dari seluruh kasus osteosarkoma. Angka kesintasan 5 tahun kurang dari 25%, dan dapat ditingkatkan hingga 60% ketika kemoterapi diberikan lebih awal. Diagnosis *low-grade central osteosarcoma* memerlukan pemeriksaan histopatologi secara menyeluruh serta teliti karena tumor ini secara mikroskopis dapat menyerupai gambaran neoplasma fibrooseus. Kami melaporkan seorang pasien anak laki-laki berusia 12 tahun dengan keluhan benjolan di wajah selama 4 tahun dengan gejala nasal discar, kongesti, epistaksis, dan rasa penuh pada telinganya. Hasil biopsi sinonasal menunjukkan suatu *inverted papilloma*. Dua bulan kemudian dilakukan maksilektomi dan pengangkatan massa keseluruhan. Secara histopatologi disimpulkan suatu *ossifying fibroma dengan low-grade central osteosarcoma. Low-grade central osteosarcoma* sendiri merupakan varian dari osteosarkoma yang jarang terjadi dan diagnosisnya seringkali sulit. Penyakit ini dapat salah didiagnosis sebagai lesi jinak, terutama *fibrous dysplasia* dan *ossifying fibroma*. Secara histomorfologi ditemukannya sel tumor atipik yang memproduksi matriks osteoid dapat digunakan untuk konfirmasi lesi tersebut merupakan lesi ganas *low-grade central osteosarcoma*. Seperti terlihat pada kasus kami, tumor dapat terdiri atas anyaman tulang imatur tersusun trabekular dan kurvilinear, yang ditepinya dijumpai gambaran *osteoblastic rimming* dengan latar belakang stroma jaringan ikat yang mana merupakan gambaran histopatologi dari suatu *ossfiying fibroma*.

Keywords:
low-grade central osteosarcoma; ossifying fibroma; sinonasal ostesarcoma; juvenile

*corresponding author: fikar@staff.uns.ac.id

INTRODUCTION

Osteosarcoma is a highly malignant bone tumor that typically develops from the metaphysis of long bones.[1] In children and adolescents, the incidence rate of the tumor is five cases per million people.[2] Less than 10% of osteosarcoma occurs in craniofacial bone.[2] Sinonasal osteosarcoma is rarer, accounting for roughly 6.5% of all osteosarcomas.[3] Moreover, only 5–6% of all osteosarcomas are low-grade osteosarcomas.[4] This rarity and its histopathological similarity with benign lesions can lead to underdiagnosis. Osterosarcoma is an aggressive tumor that is prone to both local and distant damage. Five-year survival is less than 25%, which may be improved to 60% when chemotherapy is initiated early.[5] Compared to other head and neck malignancies, like squamous cell carcinoma, sinonasal osteosarcoma has a worse prognosis rate.[6] A history of ionizing radiation exposure, fibrous dysplasia, retinoblastoma, or previous exposure to thorium oxide, a radioactive scanning agent, has all been linked to the development of osteosarcoma. Four percent of all osteosarcoma patients have a history of prior radiation therapy for other tumors or conditions.[7,8]

Osteosarcomas can be divided into several subtypes according to the degree of differentiation, location within the bone, and histological variants. These subtypes vary in imaging findings, demographics, and biological behavior. The subtypes include intramedullary which is the most common encompassing 80% of the cases and includes conventional high-grade, and low-grade central osteosarcoma.[1,8] Among paranasal subsite involved by tumor, maxillary sinus (63.8%) was the most often affected paranasal subsite by tumors, followed by the ethmoid sinuses (52%), nasal cavity (46%), sphenoid sinus (28%), and frontal sinus (20%).[9]

The low-grade central osteosarcoma diagnosis requires a meticulous histopathological examination because, histopathologically, the tumor may mimic fibro-osseus neoplasm.[5,10] The problem arises when the classic histological appearance of osteosarcoma overlaps with that of a benign fibro-osseus lesion, making the diagnosis difficult.

Ossifying fibroma is a fibro-osseus tumor of the craniofacial skeleton. It affects individuals ranging from 3 mo to 70 y.o. (frequently in the 3 to 4th decade). The tumor can produce clinical features such as facial enlargement, nasal obstruction, pain, sinusitis, proptosis, and exophthalmos. A juvenile type of ossifying fibroma is more common in the paranasal sinuses and periorbital bone, with a more aggressive clinical course and a recurrence rate of 30-58%.[11] Lee *et al.*[12] reported the case of low-grade osteosarcoma arising from cemento-ossifying fibroma in the mandible. Due to the rarity of such cases, we report a case of low-grade sinonasal osteosarcoma accompanied by juvenile ossifying fibroma in the sinonasal region.

CASE

A 12 y.o. boy presented with progressive facial enlargement in the last 4 yr. He also experienced nasal congestion, discharge, epistaxis, and fullness with ear pain. Three years earlier, the doctor in primary health care recommended surgery for the patient. The patient refused and tried herbal medication (propolis) for about 2.5 yr, but the symptoms did not improve.

The patient finally agreed to medical intervention. A head CT scan revealed a mass measuring 6x4x5 cm, occupying the nasal cavity. There was thickening and deformity of the nasal and ethnoid bone, extending to the basis cranii. There was also effacement of the hard palate. No intracerebral invasion was observed (FIGURE 1). The sinonasal biopsy was later performed and revealed an inverted papilloma. Two months after the biopsy

procedure, mass extirpation and medial maxillectomy was performed in Dr. Sardjito General Hospital, Yogyakarta and the specimen was sent to the Department of Anatomical Pathology.

Macroscopic examination reported that the tumor was pieces of ragged tissue, approximately 200 cc. The biggest specimen was 6x3x0.6 cm, and the smallest specimen was 0.4 cm in diameter, white to tan, and brittle (FIGURE 2). Microscopic examination showed woven bone with a curvilinear, trabecular arrangement, like a Chinese letter lined by an osteoblastic rimming between cellular connective tissue stroma (FIGURES 3-4). In another part, there were also infiltrating tumor cells into the connective tissue and bone around them. The tumor cells were polymorphic, spindle-to-oval, with scanty cytoplasm. Nuclei were oval to spindle, with coarse chromatin; some were hyperchromatic (FIGURES 3-4). Osteoid matrix was also found. The histopathology examination confirmed the diagnosis of low-grade central osteosarcoma accompanied by ossifying fibroma. Immunohistochemical staining showed positivity of osteocalcin with a proliferation index of Ki-67 at 10% (FIGURE 4).

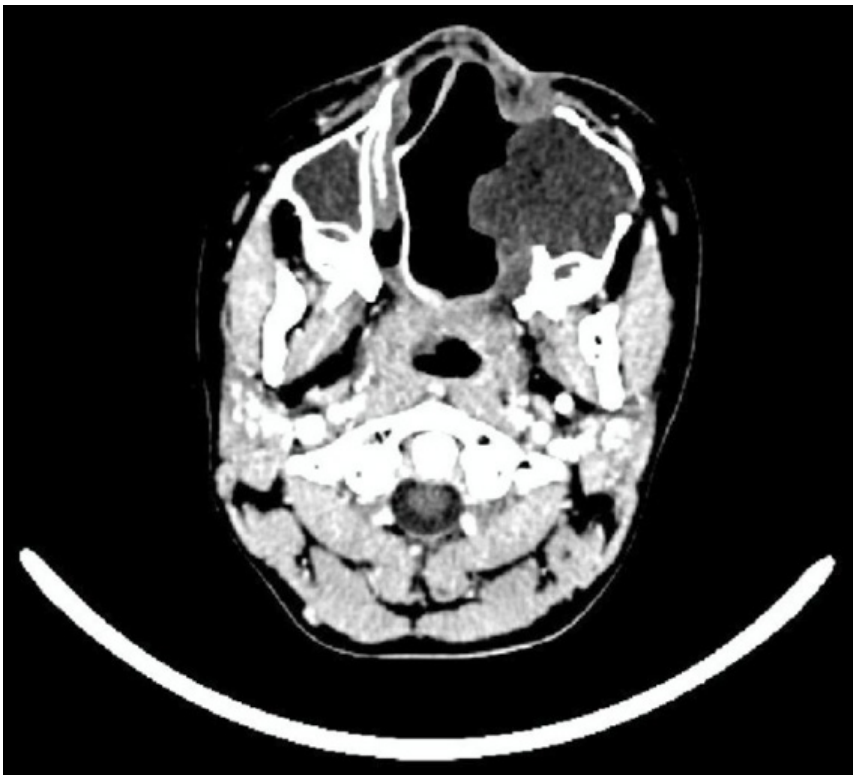

FIGURE 1. CT scan revealed isodens lesion with extension to nasal cavity and left maxillary sinus

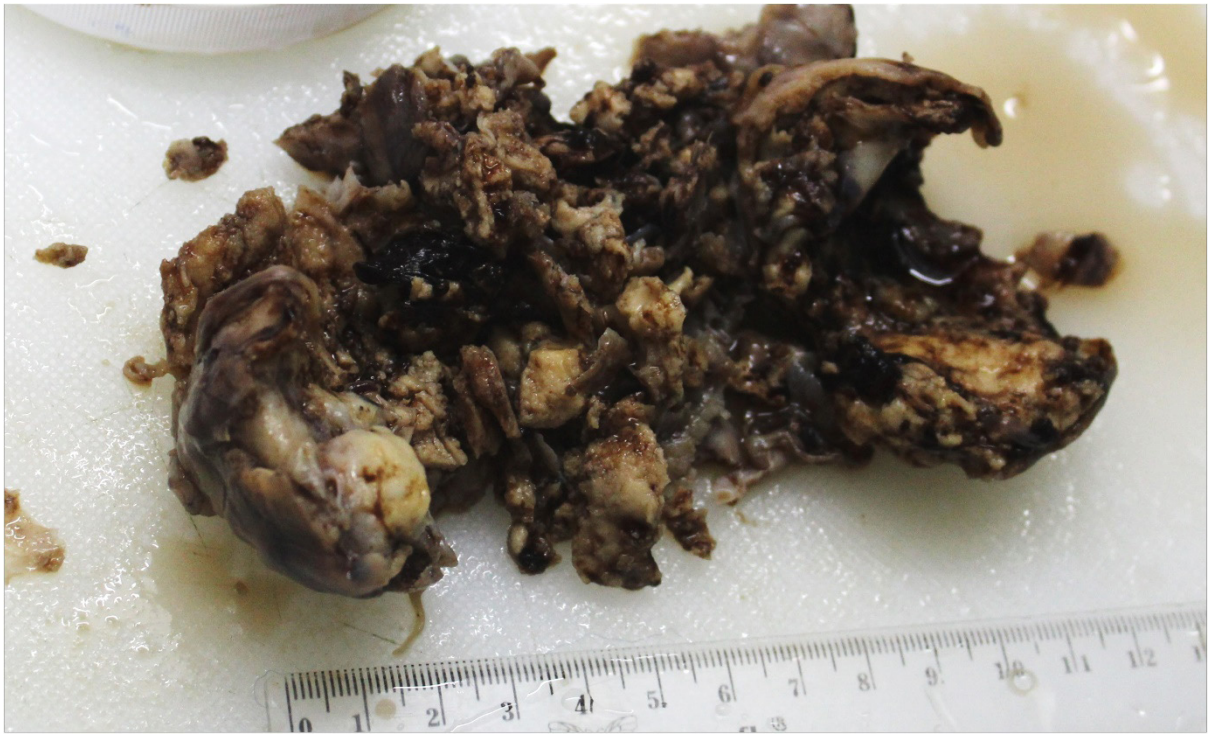

FIGURE 2. Gross examination of mass extirpation and medial maxillectomy.

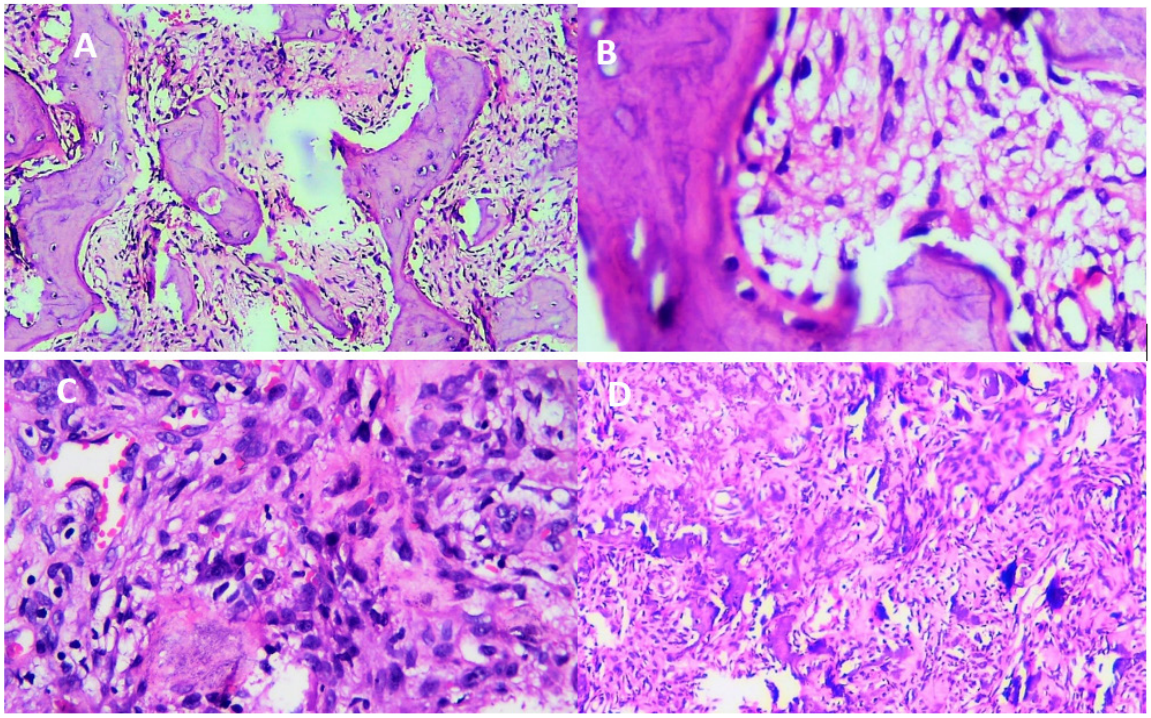

FIGURE 3. HE 100x. The part of ossifying fibroma (A &B). Curvilinear woven bone with osteoblastic rimming between cellular fibrous stroma. Tumor cells are relatively monomorphic, bland nuclei, with smooth chromatin. The part of low-grade central osteosarcoma (C&D). HE staining showed infiltrating tumor cells to connective tissue and bone around them some tumor cells are polymorph, spindle to oval, with scanty cytoplasm. Nuclei are oval to spindle, coarse chromatin, with prominent nucleoli.

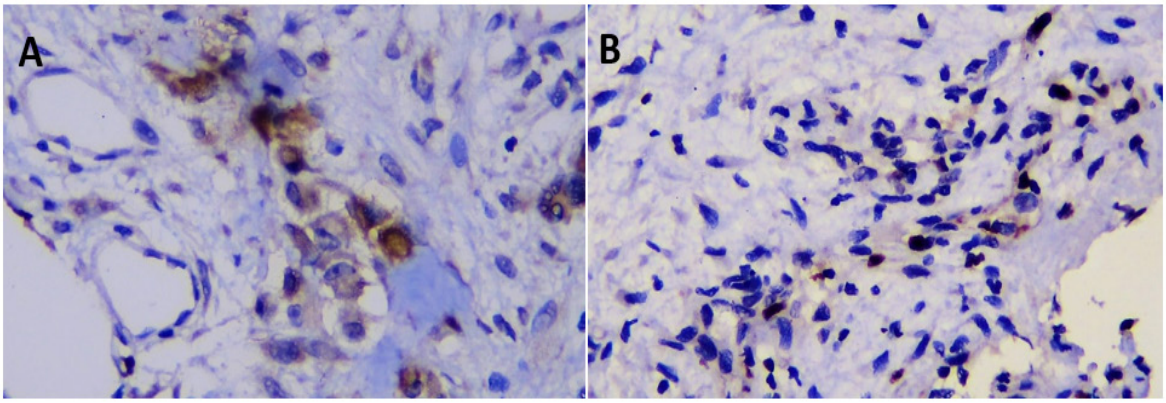

FIGURE 4. A. Positive expression of osteocalcin staining on tumor cell cytoplasm. B. Positive expression of Ki-67 staining on tumor cell nuclei.

DISCUSSION

Primary osteosarcoma in the head and neck region mostly occurs in the maxilla and mandibula, and sinonasal is an unusual site for craniofacial osteosarcoma.[1] In contrast to classical osteosarcoma of the long bones, which primarily affects adolescents and young adults, craniofacial osteosarcomas most commonly occur in the third or fourth decade of life. There has been no recognition of gender predominance.[1,8] Pediatric craniofacial osteosarcoma is extremely rare, as Hadley *et al.*[13] report in their article, with only 23 cases of cranial osteosarcoma in pediatric patients reported in the literature between 1945 and 2012, and they found that the mean age of the patients was 12.2 y.o. Our patient was 12 y.o. when diagnosed.

The term osteosarcoma refers to a heterogenous group of primary malignant neoplasms affecting bone-forming or mesenchymal tissues that have histopathologic evidence of osteogenic differentiation.[5] Histopathologic appearances of osteosarcoma, osteomyelitis, and fibrous dysplasia occupy a spectrum that may have considerable overlap. In some cases, a classic histopathologic appearance makes the diagnosis clear; however, when the picture is that of new bone formation in a background of cellular fibrous connective tissue, the diagnosis is more difficult.[5,10]

The subtypes of osteosarcoma include conventional high-grade with fibroblastic, osteoblastic, or chondroblastic differentiation, high grade surface osteosarcoma, parosteal, periosteal, and low grade central osteosarcoma. Low-grade central osteosarcoma is extremely rare and requires a meticulous histopathological examination, because, histopathologically the tumor may mimic fibro-osseus neoplasm. Histopathology features of atypical sarcoma cells that produce an osteoid matrix can be used to confirm the malignant lesion of low-grade central osteosarcoma.[5,10]

Histopathology revealed two distinct tumor entities, as demonstrated in our case. Some parts of the tumor area were suitable for ossifying fibromas, while others represent malignant atypical sarcoma cells from an osteosarcoma. Osteosarcoma may destroy connective tissue and bone boundaries. Tumor cells vary in size and shape and frequently have large hyperchromatic nuclei; bizarre tumors and giant cells are common, as are mitotic figures. The production of mineralized or unmineralized bone (osteoid) by malignant cells is essential for the diagnosis of osteosarcoma. This

finding was also seen in our case.[10,12]

Ossifying fibroma histologically consists of fibrous connective tissue of low to moderate cellularity with a trabecular pattern containing irregular bony trabeculae. A psammomatoid pattern composed of spheroid bony islands may be found. Osteoblasts rimming woven bone are inconspicuous, with occasional mitotic figures. Osteoclast-like giant cells can also be found. This finding was also seen in our case.[5]

Osteocalcin immunohistochemistry may be helpful in distinguishing osteosarcoma from other malignancies and has been proven to be sensitive but lacks specificity.[14] Very low expression of Ki-67 immunohistochemistry (< 10%) is observed in this tumor, in contrast with the cases of high and intermediate grades of osteosarcoma, that showed strong to moderate positivity of >50% and 25-50%, respectively.[15] From a therapeutic point of view, the most important factor in determining prognosis is resection with wide surgical margins, which has an 80% 5-year survival rate. In cases of low-grade central osteosarcoma, adjuvant chemotherapy or radiotherapy appear to be ineffective.[1,8]

The nasopharynx, orbit, and cranium are some of the anatomical systems that sinonasal osteosarcomas can invade. Although lung and and lymph node metastases have been recorded, haematogenous spread is less common in sinonasal osteosarcoma than in its long-bone counterpart. This tumor needs special attention because, although it is well differentiated, low-grade osteosarcomas can dedifferentiate into high-grade osteosarcomas and lead to more aggressive clinical significance.[16]

Osteosarcoma, as a secondary tumor, may arise from a preexisting benign bone disease such as Paget's disease, bone infarcts, osteomyelitis, or trauma. In our case, there is a possibility that ossifiying fibroma may trans` form into low-grade osteosarcoma, despite insufficient data for evaluating this malignant transformation. Ossifiying fibroma is a benign lesion, but sometimes it may behave in an aggressive manner and cause extensive bone destruction. In addition, there is only one reported case of low-grade osteosarcoma arising from cemento-ossifying fibroma.[12]

Current treatments for osteosarcoma include wide excision, neoadjuvant therapy, radiation therapy, and chemotherapy. Intramedullary and surface tumors of low-grade osteosarcoma with no metastasis need wide excision alone, whereas tumor located in the periosteal region need neoadjuvant therapy before wide excision. A high-grade tumor with no metastasis needs neoadjuvant therapy, restaging, wide excision of the resectable, evaluation of the chemotherapy response, and chemoradiotherapy. If there is an adequate response to chemotherapy, the same neoadjuvant therapy can be continued, whereas if there is an inadequate response to neoadjuvant chemotherapy, consider a new chemotherapy regimen, additional surgical resection, and radiation therapy. A tumor with metastasis needs metastasectomy and chemoradiation in addition to the above procedures.[2] On the patient, tumor location in the sinonasal made it more difficult to achieve a clear margin excision; therefore, close surveillance is warranted.

The NCCN guidelines suggest surveillance every 3 mo for post-op years 1 and 2, every 4 mo in post-op year 3, every 6 mo in post-op years 4 and 5, and yearly for post-op years 6 and beyond. Surveillance should include physical examination, imaging of the post-op site and chest, a PET/CT scan, and additional laboratory tests as clinically indicated.[2]

CONCLUSION

Juvenile ossifying fibroma with part of low-grade central osteosarcoma is a

rare disease. We should be aware of the rare possibility that ossifiying fibroma may transform into osteosarcoma, as shown by the presence of the two different tumor entities in our case. Careful diagnosis and regular follow up are needed for an optimum clinical outcome.

Patients with low-grade sinonasal malignancy need careful attention, especially in obtaining a representative sample, biopsy procedure, diagnosis, and treatment. Optimal clinic-radio-pathological correlation and effective communication between clinician, radiologist, and pathologist were needed to diagnose low grade osteosarcoma that occurs at less frequent sites, for example, in the sinonasal region. Early, appropriate diagnosis will prevent wasting time, resources, and opportunities to treat patients with optimal results. Close surveillance after treatment is needed in tumor cases that are located close to vital organs, since wide resection and a clear margin are difficult to achieve.

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