



Case series

A challenging diagnosis: Lesson from case series of sacral Ewing sarcoma

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ABSTRACT

Background: Ewing's sarcoma is an aggressive bone and the surrounding soft tissue cancer primarily found in children and young adults. It is mostly observed in the trunk and long bones while unusually seen in the sacrum. Sacral Ewing sarcoma has a unique anatomic limitation due to neurological structures, vertebral column, and pelvic involvement. Hence, identifying sacral Ewing's sarcoma remains a challenge.

Method: This is a case series including three patients diagnosed with Sacral Ewing's sarcoma. These three cases have been diagnosed based on clinical and radiographic examination, MRI, histopathology, and immunohistochemistry examination.

Discussion: Sacral Ewing's sarcoma remains a challenge to diagnose due to its unique anatomy site. MRI examination is sensitive to detect lesions but nonspecific. Thus, require histopathological confirmation.

Conclusion: Early diagnosis of Ewing's sarcoma is essential and we need to perform further examinations, such as immunohistochemistry examination, to confirm the diagnosis of Ewing's sarcoma.

1. Introduction and importance

Ewing's sarcoma is an aggressive bone and the surrounding soft tissue cancer primarily found in children and young adults. First described by James Ewing in 1921, Ewing's sarcoma is the second most common pediatric bone cancer after osteosarcoma with approximately 30–40% survival depending on tumor site and the presence of metastases at diagnosis. The origin of Ewing's sarcoma remains unknown. However, James Ewing reported this malignancy as an endothelioma of bone tissue that arises from perivascular lymphatic endothelium. Other investigations have introduced various origins of cells, including hematologic, mesenchymal, and fibroblastic. Recent evidence shows that Ewing's sarcoma arises from a mesenchymal stem or progenitor cells. A further definitive answer may require additional analyses [1–3].

The cell of origin of Ewing's sarcoma remains has not been clearly stated in the literature. Ewing's sarcoma is characterized by a random gene arrangement of EWS and ETS (E26 transformation-specific or E-twenty-six) gene family. The most common gene arrangement reported is t(11;22)(q24;q12), while the hybrid EWS-FLI1 gene has resulted from a gene fusion involving the EWS gene at22q12 with FLI1 gene at 11q24 for more than 80% of cases [4]. Numerous studies found that EWS-FLI1

protein fusion acts as a transcription factor. This mechanism is known to be the pathogenesis of Ewing's sarcoma. Other literature also suggested other chromosome translocation and complex gene arrangements, however, the association with the characteristic of the aggressive tumor remains unclear [5].

The predilection of Ewing's sarcoma has been reported on the trunk and long bones. The truncal skeleton Ewing's sarcoma specifically most found in the pelvis predominates, scapula, ribs, vertebral column, and clavicle. While long bone Ewing's sarcoma is mainly found in the humerus, tibia, and forearm bones. Unlike osteosarcoma, Ewing's sarcoma usually originates from the diaphysis rather than the metaphysis, whereas primary Ewing's sarcoma of the spine is considered a rare case [6,7].

Primary malignant sarcoma of the spine is an extremely rare case, contributing to roughly only 2,5–14,9% of all cases of bone malignancy [8]. A systematic review reported that cervical, thoracolumbar, and sacral spinal Ewing's Sarcoma contributed roughly 20%, 18%, and 61% in spinal Ewing's sarcoma cases accordingly [9].

The diagnosis of Ewing's sarcoma remains challenging for recent studies. The small, round, blue cells followed by a positive CD-99 antigen expression are the gold standard diagnosis of histological

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Fig. 1. Lumbosacral spine radiograph shows destructive lytic lesion, demonstrates classic findings of permeative bone destruction involving lumbosacral region.

examination in Ewing Sarcoma. Unfortunately, the CD-99 antigen itself is not purely specific for Ewing's sarcoma, the marker is also expressed for other primitive neuroectodermal tumors. Any radiologic examinations, such as Computed Tomography* (CT) scan or Magnetic Resonance Imaging (MRI), is also unable to create specific imaging for Ewing's sarcoma. On the other side, the recognition of the disease is often delayed due to the late occurrence of the symptoms [8].

Sacral involvement is rare among Ewing's sarcoma, but it should be included in differential diagnosis of low backache in children. The diagnosis remains a challenge since the diagnosis should rely on histological examination and the symptoms are not specific [5,10]. In addition, the suspicion of sacral Ewing's sarcoma requires radiological examination including MRI scans or CT scans [5]. Aggressive sacral tumors could present early but, according to previous study, there was a mean delay of 2 years from symptom onset to diagnosis [10]. Thus, the diagnosis of sacral Ewing's sarcoma is often delayed.

2. Method

We conducted a case series study from three cases of pain and lump

in the sacral region. All of them had undergone MRI examination, which revealed a lytic lesion around the sacral region with the possibility of malignancy. Each patient underwent a biopsy resulting in a malignant round cell tumor with a conclusion of Ewing's sarcoma. The three patients were brought up and discussed in the clinicopathological conference. This case series has been written following the PROCESS 2020 criteria [3].

3. Case presentation

3.1. Case 1

A 15-year-old boy with a history of a presented lump in the lower back and lower limbs weakness two months before admission. He felt pain and swelling in the back suspected due to the history of trauma while getting out of bed. A month later, the lump gets more extensive same as chicken egg size. The patient also complained of weakness, numbness, and tingling in both lower limbs and interfering the daily activities. The patient underwent an MRI examination and immunohistochemical smear biopsy. Both results showed the characteristics of Ewing's sarcoma (Figs. 1-3).

3.2. Case 2

A 10-year-old girl had typically intermittent pain on the left hip nine months before admission. The pain significantly worsens during heavy activities, with no signs of lump and fever. The patient had a history of falling on a sitting position a month before. The patient felt the pain was heavier eight months later, followed by a marble-sized lump appearing on the left hip and getting more extensive to the size of a duck egg. The pelvis MRI examination showed a bone tumor, then the core biopsy and immunohistochemistry examinations showed a mass of small round cell tumor similar to the characteristics of Ewing's sarcoma (Figs. 4-6).

3.3. Case 3

A 19-year-old woman with a history presented an increased pain in the right pelvis five months before admission. The pain felt while sitting for hours. She was massaged five times within two months by a masseur,

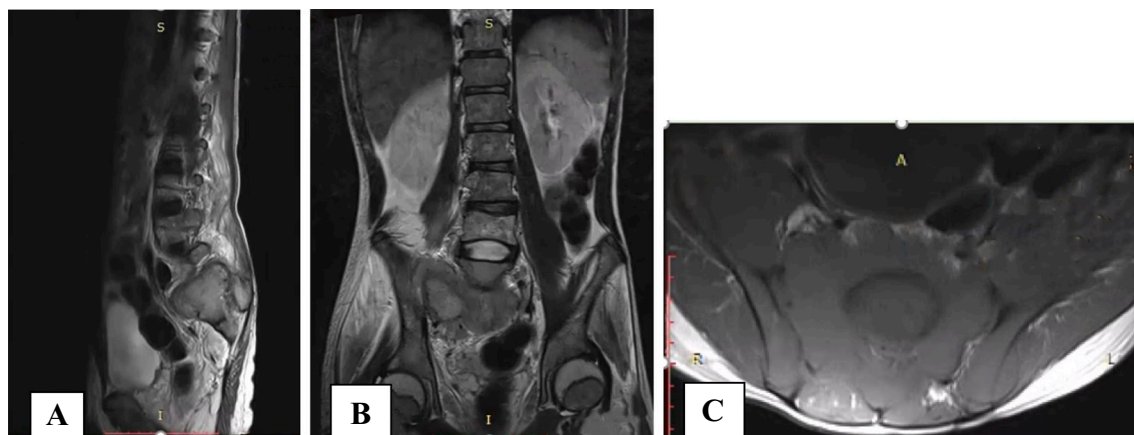


Fig. 2. MRI Examination of the LumboSacral show lumps in the lower back that caused the pain. A. Sagittal view showed the penumbra sign, a peripheral layer surrounding a cavity in either the bone marrow or adjacent soft tissues that are hyperintense in the sacrum. B. Coronal view also showed penumbra sign. C. Axial view showed the lump appearing in the sacrum with hyperintense view.

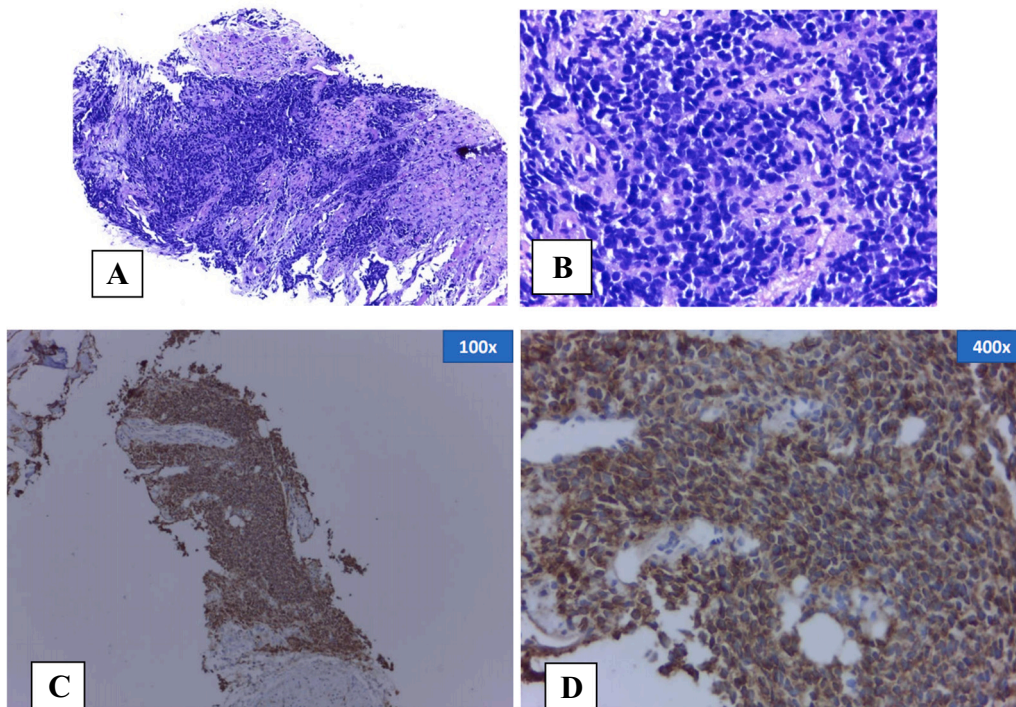


Fig. 3. A, B Hematoxylin and eosin stain of typical Ewing sarcoma, Uniform small cells with round nuclei and fine chromatin from the biopsy examination of the mass in the sacrum. C, D Result from immunohistochemistry examination of the patient that show the microscopic features of Ewing's sarcoma.



Fig. 4. Lumbosacral spine radiograph showing destructive lytic lesion, demonstrating classic findings of permeative bone destruction involving lumbosacral region.

but the pain is getting worse. Two months later, she began to notice a lump in her right pelvis accompanied by increasing pain. The patient underwent radiological examination, MRI, and biopsy examination (Figs. 7-9).

4. Discussion

Ewing's sarcoma remains a deadly form of cancer in children and young adults. Pathogenesis of the disease was associated with some random genetic arrangements and chromosomal translocation. The tumor itself arises within a defined ethnic boundary, yet only sporadic consanguinity has been reported [11]. Because of the rarity of the tumor, a remote familiarity may have evaded detection thus far. Therefore, in-depth investigation regarding the genetic epidemiology of Ewing's sarcoma might be essential to determine if the tumor was associated with a genetic predisposition. This proposed idea may only be accomplished by a thorough analysis of Ewing's sarcoma data registries in a large population. Most of extra-skeletal Ewing's sarcomas cases were reported in patients between in their first and third decade of age, and the highest incidence is in second decade [12–14].

This type of sarcoma primarily affects the bones, with rare involvement in soft tissues. The most common extraskeletal Ewing's sarcoma sites are chest wall, paravertebral muscles, buttocks, extremities, and retroperitoneal space. Similar to its counterparts in bones, extraskeletal Ewing's sarcoma is also rapid-growing with frequent distant metastases [14,15]. The spine Ewing's sarcoma is relatively rare, especially for those with sacrum involvement. Most Ewing's sarcoma in the spine results from metastasis [16].

Diagnosis in spinal Ewing's sarcoma is often delayed since the symptoms are usually not present until neurological deficits occur. This type of sarcoma usually related to resting back pain (100%) and other radiculopathy manifestations, i.e. functional limb weakness (70%) and paresthesia (50%) [14]. Similar to our primary complaints of persistent back pain with a acute increasing pain that reveals a prodromal symptom of Ewing sarcoma [11].

Ewing's sarcoma rarely involves sacral; however, it should be included in differential diagnosis of low backache in children. The diagnosis which relies on histological examination and the non-specificity of symptoms remains a challenge in making a definite diagnosis [5,10]. Aggressive sacral tumors could present early but, according to there was a mean delay of 2 years from symptom onset to diagnosis

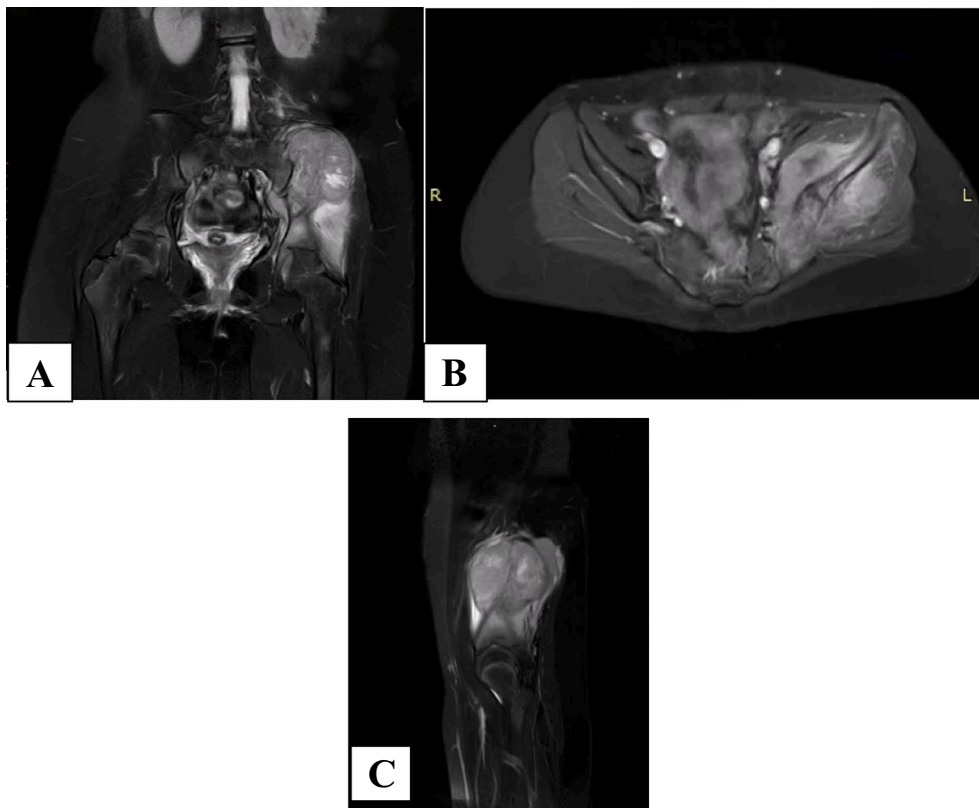


Fig. 5. The MRI Examination of the Lumbosacral. A. The anteroposterior view shows the penumbra sign, a peripheral layer surrounding a cavity in either the bone marrow or adjacent soft tissues that are hyperintense in the sacrum. B. The axial view also shows hyperintensity on the sacroiliac region. C. The lateral view shows the lump appearing in the sacrum with hyperintense view.

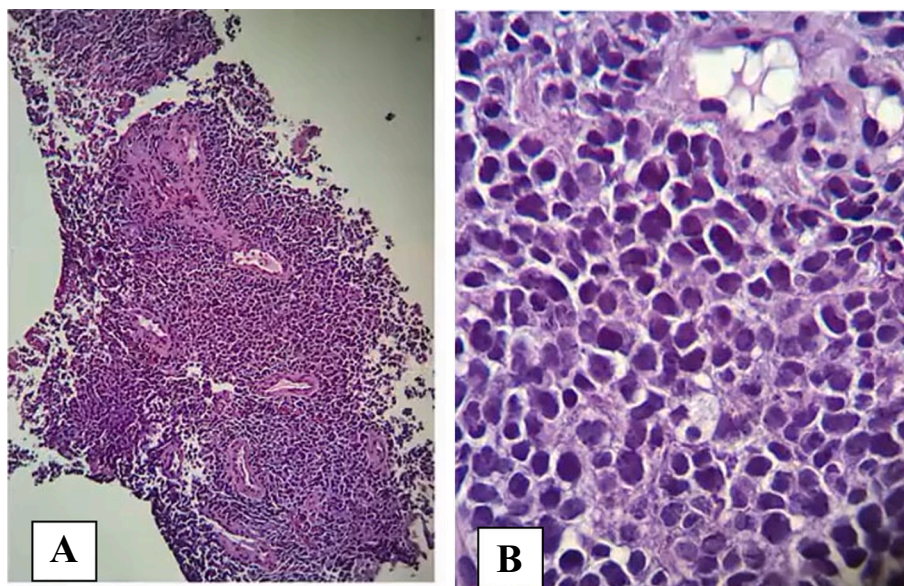


Fig. 6. Biopsy result. A. Hematoxylin and eosin stain of typical Ewing sarcoma. B. Microscopic features of Ewing’s sarcoma, Uniform small cells with round nuclei and fine chromatin.

[10]. The common symptom was low backache which lead to several differential diagnosis including tuberculosis, pyogenic osteomyelitis, lymphoma, chordoma, osteogenic sarcoma, and Ewing’s sarcoma. Diagnosis of sacral Ewing sarcoma should be suspected especially if there were lytic, sclerotic, or mixed lesions in the paraspinal soft tissue and extra dural space on the CT scan examination of the sacrum. In

addition, the suspicion of sacral Ewing’s sarcoma need radiological examination including MRI or CT scans [5]. Therefore, the diagnosis of sacral Ewing’s sarcoma is often delayed.

Also, challenges in diagnosing Ewing’s sarcoma in the spine of our patients are due to the difficulties in identifying radiographic images that might confuse to cast out the other possible differential diagnoses, i.



Fig. 7. Lumbo-sacral Spine radiograph shows destructive lytic lesion, demonstrating classic findings of permeative bone destruction involving the lumbosacral region.

e., Ewing's sarcoma involving the spine might be mistaken as a degenerative spine. Images of sacral Ewing's sarcoma are usually shows lytic, sclerotic, or mixed lesions in paraspinal soft tissue and extradural space on MRI. However, the images are not specific to Ewing's sarcoma, it shows a low to intermediate signal intensity on T1 W1 and high intensity on T2 W1 similar to the other types of osteosarcomas [17]. Many different types of tumor also complicate the early diagnosis of Ewing's sarcoma in adults, such as pseudohemangioma, aneurismal bone cyst, neuroblastoma, and Langerhans cell histiocytosis [16].

The small, blue, round cell tumors are the histological features akin to Ewing's sarcoma are hard to differentiate from neuroblastoma, malignant lymphoma, and rhabdomyosarcoma. Thus, Ewing's sarcoma is able to be distinguished by using the cell surface marker, CD99 (encoded by MIC2 gene) or Friend leukemia integration 1 transcription factor (FLI1) with immunohistochemistry. However, the sensitive marker also shows a positive result in other types of malignancies, such as neuroectodermal tumors [18,19]. Ewing's sarcoma shows a negative result on CD45, desmin, actin, or MYOD1 tests. Furthermore, this malignancy has a specific translocation in FLI1 in chromosome 11q24 and Ewing sarcoma breakpoint region 1 (EWSR1) on chromosome 22; t(11;22)(q24;q21) producing an EWSR1-FLI1 fusion transcript and protein [20]. The example of EWSR1-FLI1 gene detection can be seen from Gamberi et al. study below [4] (Fig. 10).

Song et al. [20] reported a 4-year-old girl with back pain and difficulty walking with an MRI scan that showed a mass in the spinal canal from T11 to L3/L4 levels. Molecular analysis showed translocation in t(11;22)(q24;q12), suggesting primary Ewing's sarcoma diagnosis. Similar to our first patient, the pain was the chief complaint in Ewing's sarcoma in the spine with numbness and tingling in the lower extremities. The study concluded that Ewing's sarcoma should be considered in

the differential diagnosis of patients presenting with intraspinal lesions [21].

Another study reported a 9-year-old patient with soft tissue swelling and pain in the lower back with a characteristic of piercing pain without any history of trauma. Radiographs of the sacral spine showed lobulated soft tissue mass in the intraspinal and extraspinal of the sacral region (S2-S4), and the histopathologic examination confirmed Ewing's sarcoma [22]. Meanwhile, the patient report from Srinivasalu et al. [5] also showed a 15-years-old boy with pain in the back and weakness of the left lower limb involving flexor hallucis longus and flexor digitorum longus (grade 1 power). The patient was previously suspected of TB, except the biopsy revealed Ewing's sarcoma. CT and plain radiographs of Ewing's sarcoma may show lytic, sclerotic, or mixed lesions involving paraspinal soft tissue and extradural, possibly extending to the intraspinal region. However, the radiographs imaging are not specific and presenting with a visible lump; biopsy should follow [5].

Cases of sacral Ewing's sarcoma have also been reported in the adult population. Iacoangeli et al. [17] reported a 58-year-old with worsening back pain, bilateral buttock cramping, and numbness and tingling in the left leg. Radiographic examination was not specific, but histopathological examination is indicative of Ewing's sarcoma. The patient then started radiotherapy and cycles of chemotherapy but unfortunately died a few weeks after [16].

Early diagnosis of sacral Ewing's sarcoma should be prompted despite its challenges. Weiss et al. [23], in their study, showed that axial skeletal location of Ewing's sarcoma, such as in the spine, is associated with a high hazard ratio (4.73) in predicting worse overall survival. Axial skeleton Ewing's sarcoma may be biologically different in nature than its counterparts in appendicular bones. Spinal Ewing's sarcoma is aggressive, and patients typically have a short survival rate despite comprehensive treatment. Bacchi et al. [18] also found that axial location was associated with poor prognosis in nonmetastatic Ewing's sarcoma ($p < 0.02$) [23,24].

In conclusion, sacral Ewing's sarcoma is rare, making it challenging to diagnose. The diagnosis of the disease should include radiographic imaging and subsequent biopsy to confirm. Ewing's sarcoma should be suspected in patients presenting with neurological deficits and back pain after excluding other possible differential diagnoses. Early diagnosis of Ewing's sarcoma is essential regarding its poorer prognosis compared with appendicular Ewing's sarcoma. It is recommended to perform further examinations, such as immunohistochemistry examination, to confirm the diagnosis of Ewing's sarcoma.

Availability of data and material

Data availability is provided on request.

Source of funding

This case report did not intervene with patients' treatment plans and hence did not require ethical approval.

Ethical approval

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

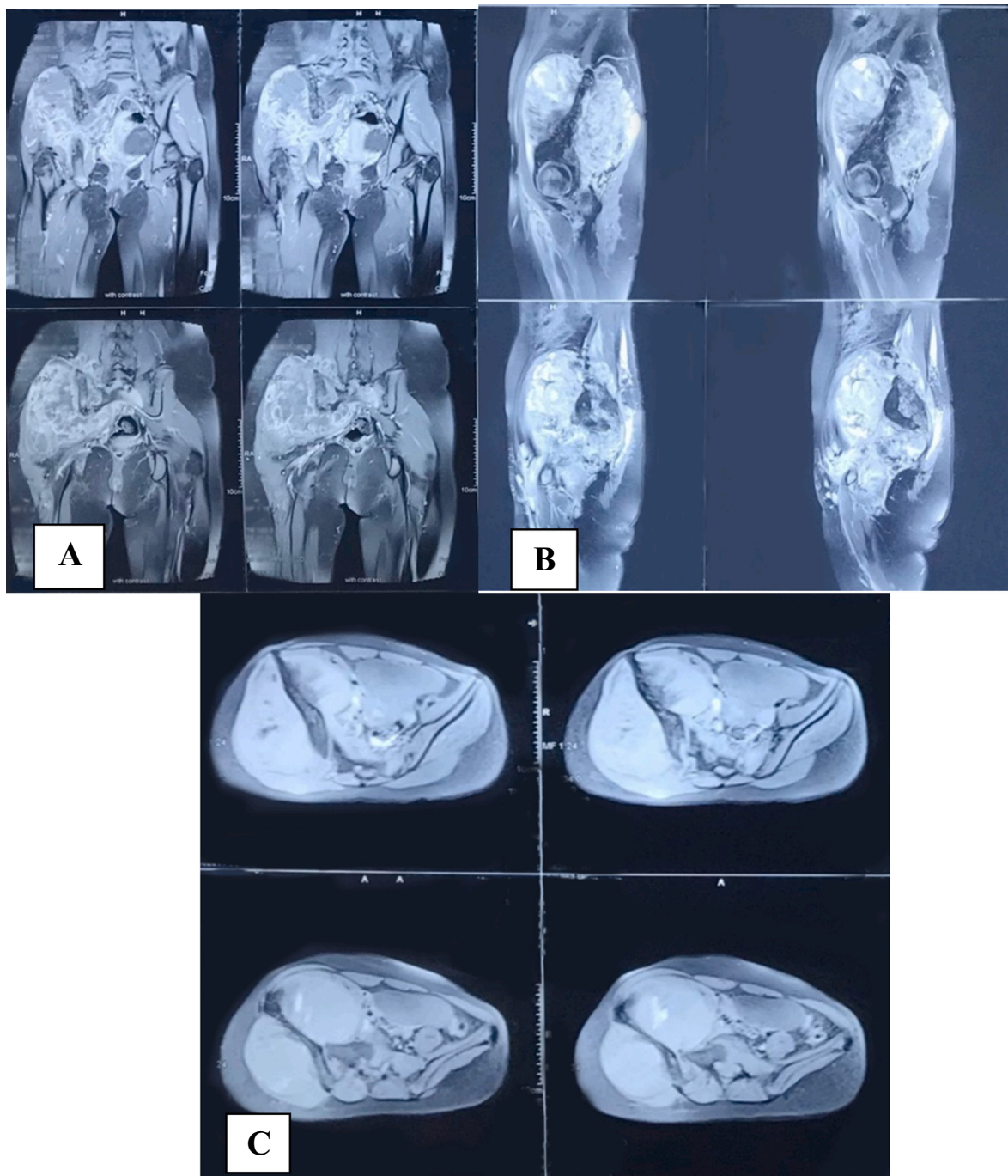


Fig. 8. The MRI Examination of the Lumbosacral. A. The coronal view showed the presence of the penumbra sign, a peripheral layer surrounding a cavity in either the bone marrow or adjacent soft tissues that is hyperintense in the lumbosacral. B. The sagittal view showed the presence of the penumbra sign. C. The axial view showed a destructive mass in the lumbosacral.

Authors' contributions

Achmad Fauzi Kamal contributes in the study concept or design, data collection, analysis and interpretation, oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team.

Sigit Daru Cahyadi contributes to the study concept or design, data collection and writing the paper.

Reza Abidin Shihab contributes to the study concept or design, data collection and writing the paper.

Didi Saputra Ramang contributes to the study concept or design, data

collection and writing the paper.

Registration of research studies

Not applicable.

Guarantor

Reza Abidin Shihab, MD.

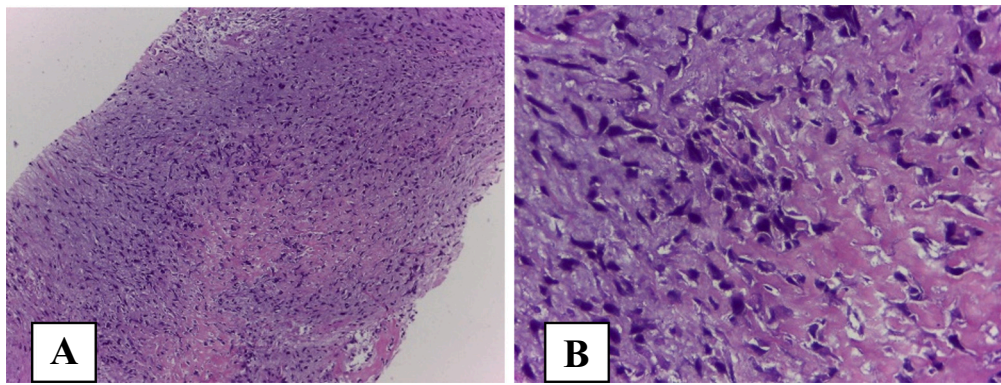


Fig. 9. Result from pathological anatomy examination from biopsy. A. Hematoxylin and eosin stain of typical Ewing sarcoma. B. The microscopic features of Ewing's sarcoma, Uniform small cells with round nuclei and fine chromatin.

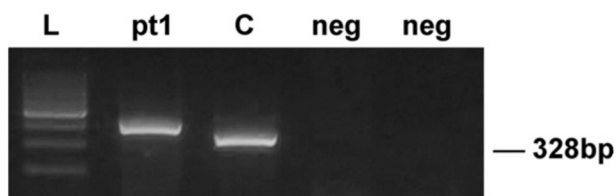


Fig. 10. Fusion gene EWSR1-FLI1 is detected by using RT-PCR [4].

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgements

The corresponding author, on behalf of all authors, declares that there is no conflict of interest.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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