Case Report

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Extra-skeletal Ewing sarcoma of the diaphragm in a young female: a case report

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Introduction and importance: Extra-skeletal Ewing sarcoma (EES) belongs to the family of primitive neuroectodermal tumors (PNET) and arises from soft tissue, with only 30 cases reported in the literature until now. Early diagnosis is crucial, and the management requires a multidisciplinary approach for better patient outcomes and survival.

Case presentation: A 20-year-old female presented to the surgical outpatient department with complaints of shortness of breath and right lower chest pain. Upon physical examination, a lipomatous lesion was observed. Ultrasound and CT scan showed a heterogeneously enhancing soft tissue mass in the right lower hemithorax causing erosion and osteolysis of the right 9th rib, involving intercostal muscles, and exerting mass effect on the underlying hemidiaphragm. Later USG-guided Tru-cut biopsy was performed to confirm the diagnosis, which reported Ewing sarcoma with CD 99, FL-1, and NKX 2.2 positive. En-bloc tumor resection along with a portion of the diaphragm was performed, and a tube thoracostomy was carried out. Chest wall reconstruction was done with mesh and a local muscle rotation flap cover. Adjuvant chemotherapy was initiated.

Clinical discussion: EES often presents with vague symptoms such as shortness of breath or abdominal or chest pain, thus making the diagnosis even more difficult. However, it has a relatively poor prognosis and thus is an important differential to rule out.

Conclusion: Extra-skeletal Ewing Sarcoma is a highly aggressive tumor that requires prompt diagnosis and treatment, with surgical resection being the first line of treatment. Adjuvant chemotherapy has also shown better outcomes.

Keywords: case report, Ewing sarcoma, neuroectodermal tumors, soft tissue tumor

Introduction

The Ewing sarcoma is primarily a neuroectodermal tumor[1]. The median age of development is usually 13 years. Fifty-five percent of patients suffering from ES are males[2]. Histologically, it is characterized by monotonous small round cells. These cells have been shown to express the following markers as well; CD 99, CD 45, Synaptophysin, Chromogranin, Vimentin, etc[3]. The most common site of metastasis of ES is the lung, bones, and bone marrow. It usually follows a hematogenous course of spread[4]. An extra-skeletal primary source of Ewing Sarcoma is a very rare presentation. It is regarded as belonging to a family of small, round-cell neoplasms called primitive neuroectodermal tumors (PNET)[5]. Thus far, there have been only 30 reported cases of extra-skeletal Ewing sarcoma. Moreover, it has been reported that around 15–40% of the patients already have metastasis at the time diagnosis is made[6]. Patients suffering from extra-skeletal Ewing Sarcoma are more likely to be already malignant on presentation. Moreover, they are more likely to arise in axial locations such as the chest and abdomen[7] and have a higher mean age of onset[8].

Ewing Sarcoma is preferably managed at a specialist center and a multidisciplinary team is employed[9]. The primary treatment of choice includes local control (either by surgery or by radiation) and systemic control by chemotherapy[10]. Various clinical trials explored the effectiveness of combinations of drugs including

HIGHLIGHTS

- EES is a highly aggressive and malignant tumor. Early diagnosis and prompt management are necessary for positive outcomes.
- A multidisciplinary approach is applied for effective management. Surgical Resection is usually considered a first-line treatment option unless there are contraindications to it, in which case, radiotherapy and chemotherapy can serve as alternatives.
- Adjuvant chemotherapy is also associated with better outcomes.
- We recommend further research to be conducted especially in understanding the pathogenesis of EES and potential molecular targets for therapeutic agents.

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doxorubicin, vincristine, cyclophosphamide, ifosfamide, etoposide, etc and recognized predictive features that can integrated to revise the protocols to minimize toxicities[11]. Prognosis is generally not good with only one-quarter of patients with an initial metastatic disease surviving[9]. EWS-FLI1 gene transformation has been shown to play a major role in the pathogenesis of Ewing sarcoma. It has shown to act as an oncogene, dysregulate gene expression for apoptosis, angiogenesis, and transform normal cells into cancerous ones[12]. Recently, there has also been new approaches to the treatment of ES that include anti-angiogenic therapy and the EWS-FLI1 oncogene[12].

We present a rare extra-skeletal Ewing sarcoma of the diaphragm in our case report. We aim to highlight the utmost importance of a multimodal team approach to manage and evaluate such rare and high-risk cases. This case report is in accordance with the SCARE criteria[13].

Case presentation

Case history / physical examination

A 20-year-old female presented to the outpatient department (OPD) of the General Surgery department in our hospital with complaints of shortness of breath for 1 week and pain in the right lower chest for 1 month. Upon examination, a lipomatous lesion was observed on the right lower chest. Her vitals were; blood pressure 130/80 mmHg, pulse rate 92/min, respiratory rate 16/min and temperature 98.6F. The rest of the systemic history and examination were normal and there was no history of malignancy in the family.

Methods (investigations, treatment)

X-ray of the chest, CT scan chest and abdomen with contrast, and abdominal ultrasound (USG) were advised. Later, a US-guided Tru-Cut biopsy was performed. The USG of the abdomen revealed a hyperechoic lesion measuring 11×9 m at the base of the right chest, subcutaneously extending intra-thoracic and causing compression of the liver and diaphragm. The CT chest with contrast reported a well-circumscribed soft tissue density mass in the right lower hemithorax, measuring $114 \times 115 \times 113$ mm in the anterior-posterior (AP), transverse (TR), and cranio-caudal (CC) dimensions. Post-contrast images showed patchy enhancement and multiple non-enhancing necrotic areas. This mass was causing erosion of the right 9th rib anteriorly. It was partially extends into the right chest wall, involving the intercostal muscles. It was also causing an indentation on the right hemidiaphragm, pushing the right lobe inferiorly and medially (Fig. 1). Laboratory values included Hb 9.3 g/

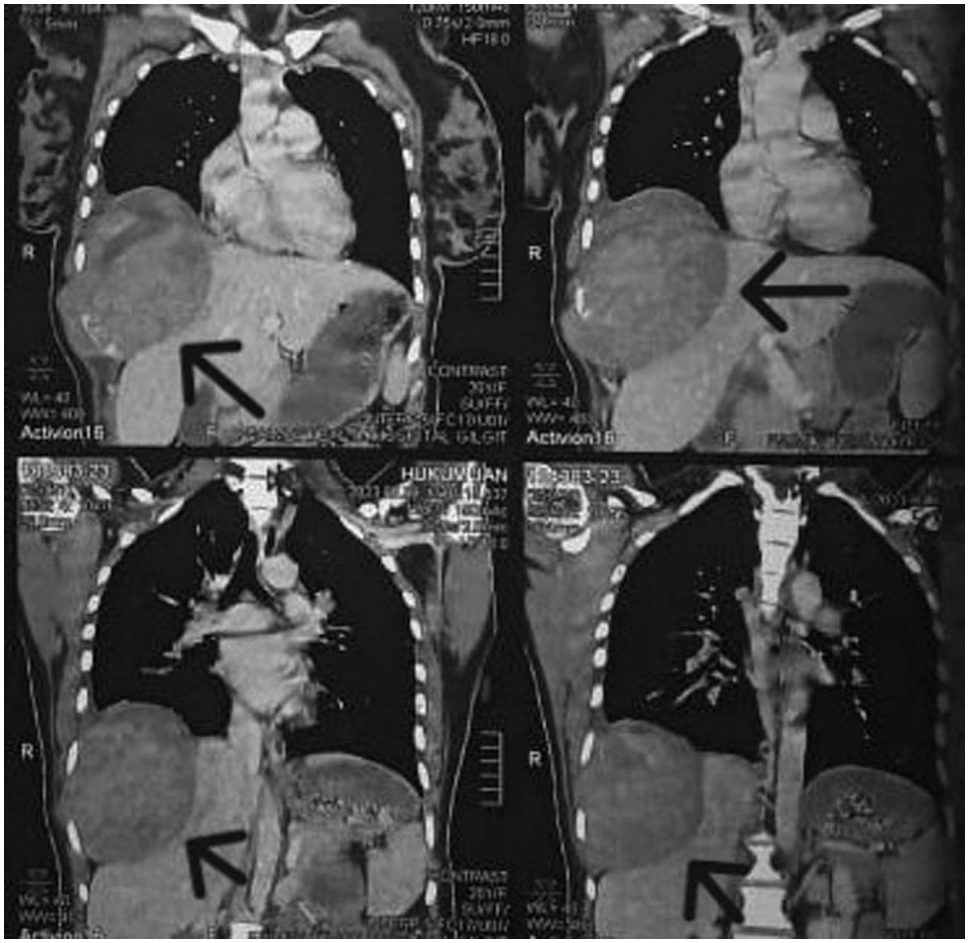

Figure 1. Different slides of coronal section of computed tomography scan chest and abdomen showing heterogeneously enhancing soft tissue density mass in the right lower hemithorax causing erosion and osteolysis of right 9th rib, involving intercostal muscles and exerting mass effect on underlying hemidiaphragm.

dl, WBCs 7.9×10^3, Platelets 201×10^3, Urea 36 mg/dl, Creatinine 0.8 mg/dl. USG-guided Tru-Cut biopsy report showing features of Ewing sarcoma, with CD 99, FL-1, and NKX 2.2 positive. Differential diagnosis based on CT Scan reporting included Askin tumor and Peripheral nerve sheet tumor.

Following the tumor board meeting, the decision was made to proceed with a local resection of the tumor. This involved performing a chest wall resection and an en-bloc tumor resection, which included the removal of the lower four ribs, intercostal muscles, overlying latissimus dorsi, and serratus anterior muscles (Fig. 2). Additionally, a portion of the diaphragm was resected, and a tube thoracostomy was performed. Chest wall reconstruction was done with mesh and local muscle rotation flap cover (Fig. 2). The resected sample was sent for histopathology which reported negative margins and confirmed the diagnosis of extra-skeletal Ewing Sarcoma histological grade 3 with features as described in (Fig. 3). Postoperative recovery was uneventful. Adjuvant chemotherapy was started using the VAC-IE regimen, consisting of Vincristine, Doxorubicin, Cyclophosphamide, Ifosfamide, and Etoposide. A total of seventeen Cycles are administered intravenously in the following doses; Vincristine 2 mg, Doxorubicin 120 mg, Cyclophosphamide 1.9 mg, Ifosphamide 2.8 gm, and etoposide 160 mg. Cycle was repeated after every 21 days.

Follow-up

The patient was assessed clinically at each cycle at the oncology center and after 10 cycles of adjuvant chemotherapy, a CT scan brain, chest, and abdomen, and a Bone scan were done, which showed no signs of recurrence or metastasis.

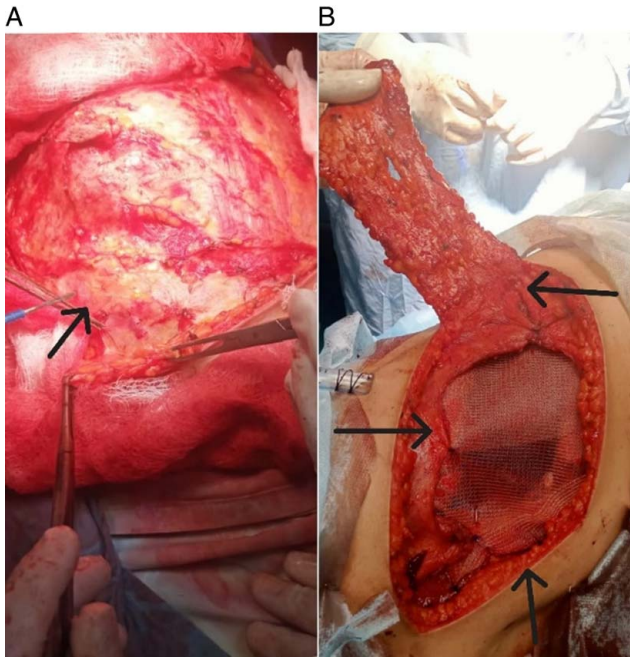

Figure 2. Figure shows the gross morphology of the tumor and the Resection technique. (A) It shows the gross morphology of the tumor perioperatively. (B) It shows the reconstruction of the chest wall using Mesh and rotation muscle flap.

Discussion

Extra-skeletal Ewing sarcoma (EES) is a rare presentation and has not been reported often in literature. Moreover, EES often presents with vague symptoms such as shortness of breath or abdominal or chest pain, thus making the diagnosis even more difficult. However, it has a relatively poor prognosis and thus is an important differential to rule out. Its diagnosis can be considered in patients who present with no primary bone lesions but have uneven intra-thoracic mass with ambiguous margins. It is especially common in adolescents and children. We present a rare case of diaphragmatic EES presenting with unusual symptoms of chest pain and shortness of breath treated by a multidisciplinary team of clinicians via local resection and subsequent chemotherapy. Our aim is to signify the importance of a multidisciplinary management team and early diagnosis of such tumors.

Primary tumors of the diaphragm often present later in life, especially in the fifth or fourth grade, and are rare. Benign primary tumors of the diaphragm are relatively common as compared to malignant ones[14]. Sarcomas of the diaphragm are exceedingly rare in the young population. Rhabdomyosarcoma, fibrosarcoma, and leiomyosarcoma are the most common tumors to present[5]. Most of the patients presenting with EES belong to a younger spectrum of the population with cases being in the second or third decade of life[15]. In our case, the patient was also relatively young with the age of 20 years. The patients' presentation is not characteristic of the disease and given the poor prognosis in most cases, early diagnosis is of supreme importance. Diaphragmatic tumor patients may present with no symptoms in one-fifth of the cases. Among the respiratory symptoms of EES, dyspnea, coughing, and chest discomfort are included. Tumors on the left side compress the stomach cardia, resulting in loss of appetite, nausea, vomiting, and difficulties in swallowing. This causes digestive problems. A physical examination may find a pleural effusion, atelectasis, or a tumor on the chest or abdomen wall[16]. Our patient, however, only had pain in the lower chest and dyspnea.

Primary EES is characterized by a massive heterogeneous mass. It also has features of frequent local invasion or compression of neighboring organs on contrast-enhanced CT or magnetic resonance imaging (MRI). More than half of these lesions are at least 20 cm or more on diagnosis[17]. Our case had an 11×9 cm hyperechoic lesion that caused compression of the liver and diaphragm. Large necrotic foci and heterogeneous areas of enhancement are present in most instances. While local invasion of neighboring organs is frequently reported, very well-defined borders are only present in rare situations[18]. Similarly, in our case, post-contrast images showed enhancement in patches of areas and multiple hypoechoic necrotic areas as well. In another case, the CT scan showed necrotic cysts and a mild heterogenous enhancement. It was also emphasized that the CT scan can show the dimensions, volume, and characteristics of the soft tissue mass. These play a pivotal role in the management plan[19]. Definitive diagnosis, however, is achieved by examining histopathology, which shows poorly differentiated, round, small blue cells, and immunological analysis, which is positive for CD 117, CD 99, FL-1, and vimentin[20]. Our patient also showed histopathological features of ES and was positive for CD 99 and FL-1 on immunohistological analysis.

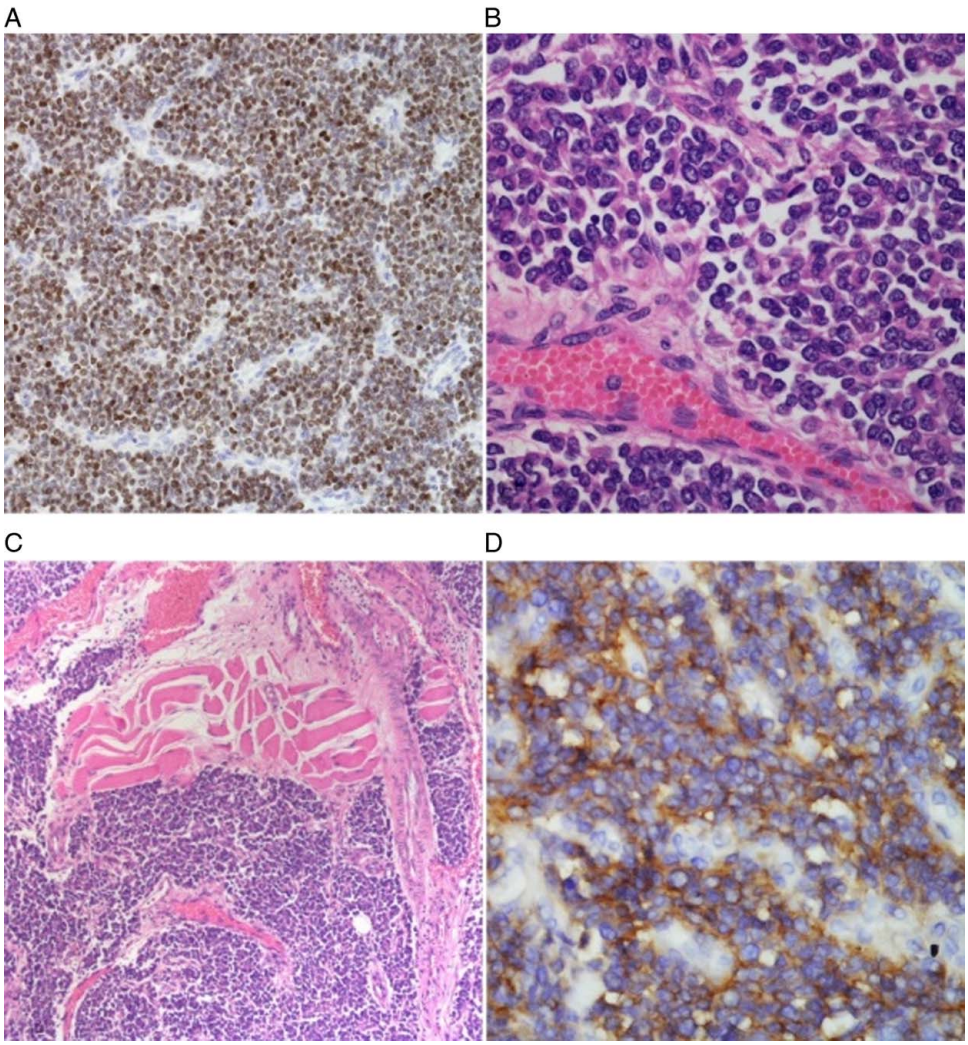

Figure 3. Histopathological evaluation of specimen. (A) Photomicrograph shows NKX 2.2 nuclear positivity on immunohistochemistry. (B) It shows a high power view of the uniform hyperchromatic cells (400 ×). (C) It shows a small round blue cell tumor infiltrating skeletal muscle (200 ×). (D) It shows membranous positivity for CD 99 on immunohistochemistry.

EES has a 10–25% chance of being metastatic on diagnosis. Metastatic disease is associated with a poor prognosis. Moreover, age (especially being above 40) and tumor size (a diameter of at least 8 cm or more) are the most important prognostic factors associated with mortality and adverse outcomes[18]. According to the guidelines published by the National Comprehensive Cancer Network (NCCN), the recommended treatment is local, which can include surgery (which is the gold standard), or radiation plus systemic therapy (chemotherapy)[21]. Surgery should be performed with clear negative margins. The disease stage has a profound effect on the outcomes after surgical debridement. After resection, approximation or prosthetic repair of the diaphragmatic edges can be done[19]. We also performed surgical debridement in which a significant portion of the diaphragm and chest wall was removed. Chemotherapy used before surgery is attempted to reduce the tumor completely or partially if it is unresectable. Radiation can also be used for unresectable tumors or those with a poor histological response[20]. Chemotherapy although relatively effective, has shown to have a 70% relapse rate within 2 years of diagnosis[20]. However, vincristine, actinomycin D, and cyclophosphamide are the chemotherapeutic agents that have shown positive results against EES. The current relapse-free survival for chemotherapy is estimated to be around 55% at 5-year intervals[9]. Our patient was treated with the VAC-IE regimen, which contains vincristine, actinomycin D, and cyclophosphamide. These drugs are then followed by ifosfamide, and etoposide phosphate. The VAC-IE regimen has been reported to have positive outcomes in EES and has been used as a first-line treatment regimen[22]. However, some cases which do not respond to VAC-IE, can be treated by gemcitabine, and dacarbazine regimen as second-line treatment option[22].

Conclusion

In conclusion, EES is a highly aggressive and malignant tumor. Early diagnosis and prompt management are necessary for

positive outcomes. A multidisciplinary approach is applied for effective management. Surgical Resection is usually considered a first-line treatment option unless there are contraindications to it, in which case, radiotherapy and chemotherapy can serve as alternatives. Adjuvant chemotherapy is also associated with better outcomes. As in our case, postoperative recovery was uneventful, and four months after chemotherapy, the patient is fully stable. We recommend further research to be conducted especially in understanding the pathogenesis of EES and potential molecular targets for therapeutic agents.

Key clinical message

EES is a highly aggressive malignant tumor and it should be kept in the differential diagnosis in case of masses of the axial region of the body as it needs prompt diagnosis and treatment. USG Abdomen and CT Scan shows a mass and a tru-cut biopsy used for diagnosis.

Ethical approval

Written Informed consent was taken from the patient for publishing this case report.

Consent

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

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Author contribution

The manuscript has been read and critically reviewed by all authors. Individual contributions include conception and data acquisition. M.I.: conception and writing. H.A.D.: writing and review. M.F.: writing and review. F.S.: writing and editing. A.J.: writing and data acquisition. T.D.: review and editing. T.D.: editing and supervision. S.H.: review and editing. N.M.: editing and supervision.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

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