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Primary Adrenal Ewing Sarcoma: A Systematic Review of the Literature

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Abstract

BACKGROUND

Ewing sarcoma is a malignant neoplasm of neuroectodermal origin which is commonly observed in children and young adults. Musculoskeletal system is the main body system that is impacted with rare alteration seen in the visceral organs and particularly the adrenal.

AIM

To present a comprehensive review of primary adrenal Ewing sarcomas, with emphasis on diagnosis, therapy and oncological outcomes.

METHODS

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. PubMed/MEDLINE, EMBASE and GoogleScholar bibliographic databases were searched to identify articles, which spanned from 1989 to 2022 and included patients with Ewing Sarcoma/Primitive neuroectodermal tumor (ES/PNET) of the adrenal

gland. PubMed, GoogleScholar and Embase medical databases were searched, combining the terms “adrenal”, “Ewing sarcoma” and “primitive neuroectodermal tumor”. Demographic, clinical, pathological and oncological data of patients were analyzed on SPSS.

RESULTS

A total of 52 studies were included for review (47 case reports and 5 case series) with 66 patients reported to have primary adrenal Ewing sarcoma. Mean age at diagnosis was 26.4±15.4 years (37.9% males, 57.6% females, sex not reported in 3 cases). The most frequent complaint was abdominal/flank pain or discomfort (46.4%) followed by palpable mass (25.0%, and the average duration of symptoms was found to be 2.6±3.1 mo. The imaging modality of choice was CT scan (81.5%), followed by MRI (20.4%). Preoperative staging revealed that 17 tumors (27.9%) were metastatic and 14 patients had inferior vena cava or renal vein neoplastic thrombus at initial diagnosis. Open adrenalectomy was performed in the majority of cases (80.0%), out of which 27.9% required more extensive resection. Minimally invasive surgery was attempted in 8.2% of the tumors. Complete surgical resection (R0) was achieved in 89.4% of the patients. Adjuvant therapy was administered to 32 patients, in the form of chemotherapy (62.5%), radiotherapy (3.1%) or combination (34.4%). Median overall survival was 15 mo and 24-month overall survival was 40.5%.Median disease-free survival was 10 mo and 24-month disease-free survival was 33.3%.

CONCLUSION

The significant progress in molecular biology and genetics of Ewing sarcoma does not reflect on patient outcomes. Ewing sarcoma remains an aggressive tumor with poor prognosis and high mortality.

Key Words: Ewing sarcoma, Primary adrenal tumor, adrenalectomy

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Core Tip: Primary adrenal Ewing sarcoma is uncommon with 66 cases reported in the literature since 1989. Patients usually present within the first year from the initiation of symptoms, most frequently complaining of abdominal/flank pain or discomfort, followed by palpable mass. Open adrenalectomy is the procedure of choice, while minimally invasive techniques are anticipated to be performed more frequently in the following years. Regardless of the technique, R0 resection is achieved in the vast majority of cases. The significant progress in molecular biology and genetics of Ewing sarcoma over the past decade does not reflect on patient outcomes. Ewing sarcoma remains an aggressive tumor with poor prognosis and high mortality.

INTRODUCTION

First described by James Ewing in 1921 as "diffuse endothelioma of bone," Ewing sarcoma (ES) is the second most common primary bone malignancy during childhood and adolescence [1,2]. Along with primitive neuroectodermal tumors (PNET) and Askin tumors, Ewing sarcomas belong to the Ewing sarcoma family of tumors (ESFT). ESFT are aggressive childhood cancers, which histollogically belong to the small round blue cell sarcomas [3].

Although the cell of origin of Ewing sarcoma remains unknown, ESFT tumors are characterized by chromosomal translocation between the TET/FET family genes and ETS (E26 transformation specific) family genes [4]. Approximately 85% of Ewing sarcomas exhibit the reciprocal translocation t(11;22)(q24;q12). This genetic alteration results in the chimeric fusion protein EWSR1-FLI1, which allows the N-terminus of EWSR1 and the C-terminus of FLI1 to bind transcriptional complexes and target genes. The target genes are involved in tumor cell immortalization, angiogenesis, cancer stemness, tumor growth, chemotherapy resistance, transcriptional regulation,

and cell-to-cell signaling. NR0B1 (DAX1), GLI1 and FOXO1 have been shown in literature to be the genes involved in the tumorigenesis of Ewing sarcoma [4].

The majority of ES/PNET tumors are found in the skeletal system, with only 10-20% arising in extraskeletal sites [5]. Visceral and particularly adrenal occurrence is even more infrequent. The morphology between ESFT may vary; however skeletal and extra-skeletal ESFT are molecularly indistinguishable [6]. Despite recent advances in molecular biology, therapeutic protocols are not standardized due to limited knowledge and are derived from other types of sarcomas. The aim of the present study is to present an up-to-date, systematic review of the literature on primary adrenal ES/PNET, with emphasis on diagnosis, therapy and oncological outcomes.

MATERIALS AND METHODS

A systematic review of the English literature was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement, [7]. PubMed/MEDLINE, EMBASE and GoogleScholar bibliographic databases were searched to identify patients with ES/PNET of the adrenal gland spanning 1989 to 2022. The keywords "Ewing sarcoma", "primitive neuroectodermal tumor", "PNET" and "adrenal" were used in all possible combinations. Further, the reference lists of all eligible papers were assessed for additional articles.

All study designs except conference abstracts and commentaries were considered eligible. Both adult and pediatric cases were included in the review. Non-English articles were excluded. Titles and abstracts of all articles from the initial search were independently screened by two authors. Articles, including case reports, case series, observational and clinical tries studies, were considered eligible for full text review, as long as they reported on cases of primary ES/PNET. Any discrepancies were arbitrated by all authors. A flow chart of search strategy is shown in Figure 1.

For each eligible patient, demographic data (age, sex), clinical characteristics (presenting symptom, duration of symptoms, hormone hypersecretion, imaging modalities, size, laterality), treatment (preoperative staging, neoadjuvant treatment,

extent of surgery, adjuvant treatment), histopathology (completeness of resection, immunohistochemistry, molecular testing) and oncological outcomes (overall and disease-free survival) were collected.

Statistical analysis was performed on SPSS, version 29.0. All data were tabulated and outcomes were cumulatively analyzed. Continuous variables were expressed as mean±standard deviation, while categorical variables were expressed as frequencies or percentages. Kaplan-Meier survival analysis was applied to calculate 24-month overall and disease-free survival. A descriptive approach was followed, due to limited data.

RESULTS

Fifty-two studies (47 case reports and 5 case series) were included in the final analysis, describing a total of 66 patients (Online resource) [8–59]. The demographic and clinical characteristics are shown in ***Table 1***. As shown in figure 2, majority of the reported cases arise from China, United States and India. Twenty-five patients were males (37.9%) and 38 were females (57.6%) (sex not reported in 3 cases). Mean age at diagnosis was 26.415.4± years (range 2-74). The most frequent complaint was abdominal/flank pain or discomfort (26 cases, 46.4%) followed by palpable mass (14 cases, 25.0%). In 10 patients (17.9%), the tumor was an incidental finding during imaging studies for an unrelated reason. Mean duration of symptoms was 2.63.1± mo (range 2 days to 1 year). Preoperative hormone panels were reported in 42 patients and hormonal hypersecretion was observed in 5 cases (11.9%). The imaging modality of choice was CT scan (44 cases, 81.5%), followed by MRI (11 cases, 20.4%). Further imaging with PET-CT was required in 6 cases (11.1%) (data not reported in 12 cases). Mean tumor size at diagnosis was 11.44.8± cm (range 3-24cm). 27 patients had right-sided tumors , 28 patients had left-sided tumors (48.2%, 50.0% respectively), and one patient had bilateral (1.8%) (data not reported in 10 cases).

Preoperative staging revealed that 17 tumors (27.9%) were metastatic at initial diagnosis, and 14 patients (23.0%) presented with inferior vena cava or renal vein neoplastic thrombus. Ten patients (18.9%) received neoadjuvant chemotherapy

preoperatively. Operative and pathological characteristics are shown in ***Table 2***. Open adrenalectomy was the procedure of choice in majority of cases (48 cases, 80.0%). Of the patients in the open adrenalectomy group, 17 patients (27.9%) required more extensive resections (usually ipsilateral nephrectomy). Minimally invasive laparoscopic and robotic approaches were attempted in 4 (6.6%) and 1 case (1.6%) respectively. Seven patients (11.7%) underwent biopsy instead of resection. Complete surgical resection (R0) was achieved in 89.4% (42/47). Immunohistochemistry stain for CD99 was positive in 98.4% (60/61) of patients. Molecular testing for the translocation EWSR1-FLI1 was performed in 27 patients, all of which were positive. Adjuvant therapy was reported in 32 patients, in the form of chemotherapy (62.5%), radiotherapy (3.1%) or chemoradiotherapy (34.4%).

Survival data were available for 42 patients. Median overall survival was 15 mo (95%CI 9.4-20.6). 24-month overall survival was 40.5%. Median disease-free survival was 10 mo (95%CI 4.3-15.7). 24-month disease-free survival was 33.3%.

DISCUSSION

Ewing sarcoma is an aggressive primary osseous tumor [60]. Extraskeletal sites involving soft tissue and visceral tumors constitute only 10-20% of the Ewing sarcomas. Soft tissue ES/PNET can be found in the muscle, connective tissue, lymph nodes, and other tissue of mesenchymal origin. Visceral ES/PNET sites include the lungs, gastrointestinal tract, prostate, brain, endometrium, thyroid and adrenal gland [45]. Our review is the first systematic review focusing on primary adrenal ES/PNET. This study yielded 66 cases between 1989 and 2022, showcasing the low prevalence of this disorder.

Clinical presentation of ES/PNET varies depending on the location of the tumor. A large, rapidly growing, solitary mass, can cause mass effects or invade nearby structures. Symptoms include constitutional symptoms, such as fever, weight loss, anorexia, pain and bleeding [61]. Our study showed that pain and discomfort were the primary complaints, followed by palpable mass.

All patients in our study were diagnosed within one year from onset of symptoms (mean duration 2.6 mo). Half of the patients were found to have metastasis or IVC/renal vein neoplastic thrombus upon the time of diagnosis. This shows that diagnosis typically occur when these tumors have reached an advanced stage, which may explain its aggressive nature. Only 17.9% of our cases were diagnosed incidentally, which comes in contrast to other adrenocortical tumors [62].

CT scan, MRI and PET-CT are the first line imaging modalities performed to detect the tumor. Adrenal ES/PNET can be demonstrated as a large size, nonfunctional mass [61]. However, imaging is limited to staging of the patient, differentiate metastatic from primary ES/PNET, and to assist with the surgical planning.

Tissue examination, immunohistochemical and genetic tests are necessary for diagnostic purposes. Utilizing histopathology, ES/PNETs can be differentiated from other adrenocortical carcinomas. ES/PNETs are seen as small round cell tumors. The 32-kDa cell surface glycoprotein has also demonstrated significant use as a screening tool given the high sensitivity (as high as 95%), although specificity is low[63]. Immunohistochemical staining for CD99 is essential to support the diagnosis of ES/PNET from other small round cell tumors. In our review, immunohistochemistry stain CD99 was tested in the majority of the cases assisting in diagnosis (61 cases). Molecular testing to identify the most common mutations, such as t(11;22)(q24;q12) (80% to 90% of ES/PNET), t(21;12)(22;12) (10%), could provide meaningful data for diagnostic purposes. However it is currently not the standard of care.

Specific instructions for the treatment of ES/PNET have not been published until today. In majority of cases, these tumors are treated according to the soft tissue sarcoma guidelines. These guidelines are published by the European Society of Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), which includes recommendations for the treatment of visceral sarcomas[64,65]. According to the guidelines, surgical excision with negative surgical margins (R0) is the preferred initial treatment. If R0 margins are not obtained with the index procedure, a second excision can be performed. Planned close margins or even microscopically positive margins (R1)

may be acceptable in certain cases, to preserve critical neurovascular structures. Post-operative radiation should be considered in tumors with R0 or R1 margins in order to reduce recurrence. This is especially indicated when the soft tissue tumor margin or the microscopic margin are positive proximal to bone tissue, major blood vessel or major nerves. Other adjuvant options include systemic therapy and/or chemotherapy. Neoadjuvant treatment, with radiation and/or systemic treatment, is performed in tumors deemed unresectable, to downsize the cancer or provide palliative measures.

In our review, the majority of the patients were treated surgically in accordance to the existing guidelines. Open adrenalectomy (80.0%) or more extensive resection (27.9%) were the procedures performed most frequently. Laparoscopic or robotic surgery was elected in a small number of tumors (8.2%). These were observed mostly in the last decade, although this is anticipated to become more frequent in the future, as technology advances and minimal invasive surgical techniques become more dominant. Neoadjuvant treatment was utilized in 18.9% of patients, to downsize the tumor, prior to surgical excision. Negative margins were obtained in the vast majority of the patients (89.4%). Adjuvant therapy was performed, mostly with chemotherapy or chemoradiation, in order to eliminate micrometastases and increase the 5-year survival rate [66].

Despite multisystem treatment modalities, average survival rate was found to be approximately 15 mo in our study. Less than half of the population demonstrated 24-month survival and one-third of patients were deemed free of disease at that time. This shows the high recurrence rate of the disease.

Research in Ewing sarcoma during the last years has focused on the identification of DNA fragments, which could potentially detect and distinguish between different cancer types and subcategories, monitor disease progression over time, as well as estimate survival and relapse probabilities at the time of diagnosis[67]. In addition, artificial intelligence has led to the development of large databases, biobanks and radiomics. In the future, both biomarkers and artificial intelligence science are anticipated to assist with stratifying patients into specific groups by creating patient

profiles who share common features. These tools will lead into the development of individualized treatments and prognostic treatment-response scores in chemotherapy and/or radiotherapy[68,69].

CONCLUSION

Primary adrenal Ewing sarcoma is uncommon with 67 cases reported in the literature since 1990. Diagnosis is usually achieved within one year from the onset of symptoms. Open adrenalectomy has been the procedure of choice, although minimally invasive techniques are anticipated to be performed more frequently in the near future. Recurrence rate within 24 mo is quite high, which proves the aggressive character if the tumor. The significant progress in molecular biology and artificial intelligence promises big achievements in the future in terms of diagnosis and treatment of Ewing sarcoma.

ARTICLE HIGHLIGHTS

Research background

Ewing sarcoma is an aggressive malignant primary osseous tumor, which is commonly observed in young population. Visceral organs and particularly adrenals are rarely impacted.

Research motivation

Therapeutic protocols for the treatment of ES/PNET are not standardized and these tumors are treated according to the soft tissue sarcoma guidelines of ESMO and NCCN, due to limited knowledge.

Research objectives

The aim of the present study is to present an up-to-date, systematic review of the literature on primary adrenal ES/PNET, with emphasis on diagnosis, therapy and oncological outcomes.

Research methods

A systematic review of the literature was performed according to the PRISMA 2020 statement. PubMed/MEDLINE, EMBASE and GoogleScholar bibliographic databases were searched to identify articles that included patients with ES/PNET of the adrenal gland from 1989 to 2022. Demographic, clinical, pathological and oncological data of patients were analyzed on SPSS.

Research results

Fifty-two studies were included in the current systematic review, describing a total of 66 patients. Mean age at diagnosis was 26.4 years and the most frequent complaint was abdominal or flank pain/ discomfor. At the time of diagnosis, average tumor size was 11.4 cm. 27.9% of the tumors were metastatic and 23.0% had inferior vena cava or renal vein neoplastic thrombus. Open adrenalectomy was the procedure of choice (80.0% of patients), and a more extensive resection was required in 27.0% of these patients. Immunohistochemistry stain for CD99 was positive in 98.4%, and molecular testing for the translocation EWSR1-FLI1 was found positive in all the patients that it was tested. Median overall survival was 15 mo and 24-month overall survival was 40.5%.

Research conclusions

Primary adrenal ES/PNET is a tumor with low prevalence. Diagnosis typically occurs when tumor has reached an advanced stage. Immunohistochemical staining for CD99 is essential to support the diagnosis of ES/PNET from other small round cell tumors. These tumors are treated according to the soft tissue sarcoma guidelines of ESMO and NCCN until today, with surgical excision with negative surgical margins (R0) being the preferred treatment of choice, when it is feasible. Unfortunately, the disease has high recurrence rate, and relatively low survival rate.

Research perspectives

In the future, minimally invasive techniques will be used more frequently in the surgical treatment of primary Ewing adrenal sarcoma. In addition, research in biomarkers and artificial intelligence science will assist with stratifying patients into groups, and lead to the development of individualized treatments and prognostic treatment-response scores in chemotherapy and/or radiotherapy.

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