AACE Clinical Case Rep. 8 (2022) 69–72

Contents lists available at ScienceDirect

AACE Clinical Case Reports

journal homepage: www.aaceclinicalcasereports.com

Case Report

Rapidly Fatal Ectopic Adrenocorticotropic Hormone Syndrome in a 9-Year-Old Girl With Ewing Sarcoma

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ARTICLE INFO

Article history:
Received 3 May 2021
Received in revised form
15 September 2021
Accepted 24 September 2021
Available online 1 October 2021

Key words:
ectopic ACTH
Ewing sarcoma
pediatric

ABSTRACT

Background: Ewing sarcoma (ES) with ectopic adrenocorticotropic hormone (ACTH) syndrome (ectopic ACTH) is extremely unusual. This report details the first case in English literature of pediatric ES involving the proximal aspect of the humerus with florid ectopic ACTH.

Case Report: A 9-year-old girl presented with mooning of the face and abdominal distension for the past 5 months with an unremarkable history. Her serum cortisol level measured at 8 AM was 42 μg/dL (reference range, 4.3-22.4 μg/dL). Serum ACTH level of 225 pg/mL (reference range, 10-46 pg/mL) suggested ACTH-dependent Cushing syndrome. Her serum cortisol level after the overnight dexamethasone suppression test was 60 μg/dL (reference value, <1.8 μg/dL), suggesting nonsuppressibility. The high-dose dexamethasone suppression test was nonsuppressible, suggesting ectopic ACTH secretion. Findings of magnetic resonance imaging of the brain were normal. Chest x-ray demonstrated a lytic lesion in the left humerus. Magnetic resonance imaging and 3-dimensional computed tomography scans of the left shoulder showed an expansile lesion in the proximal aspect of the humerus. A tru-cut bone biopsy with histopathology and immunostaining revealed clusters of small round cells with a mitotic index of 6/10 hpf to 8/10 hpf. CD99 staining confirmed ES. Ketoconazole was initiated. She received 1 cycle of chemotherapy with cyclophosphamide, vincristine, and doxorubicin and succumbed to the illness 1 week after chemotherapy.

Discussion: Ectopic ACTH in the pediatric age group is rare and, coupled with the underlying etiology as ES, makes this case unique. Only 4 cases of ectopic ACTH with ES have been previously reported in the tibia, retroperitoneum, ischiopubic rami, and ribs. This is the first case of ES to have its origin in the humerus with ectopic ACTH.

Conclusion: This case highlights an atypical presentation of ectopic ACTH caused by ES arising from the humerus. The etiology of ectopic ACTH as ES was confirmed by chance radiographic evidence of a lytic humerus lesion rather than symptoms.

Introduction

Ewing sarcoma (ES) comes under a spectrum of malignancies known as the ES family of tumors. The annual incidence of ES is 2.93 children per million. These develop most commonly in the pelvis (25%), femur (16.4%), ribs (12%), and humerus (4.8%).[1] A peak incidence of ES occurs during the second decade of life with >90% of patients aged between 5 and 25 years.[2] Tumors with ectopic ACTH syndrome (ectopic ACTH) comprise <1% of all adolescents presenting with Cushing syndrome.[3] Neuroblastomas or neuroendocrine tumors in infancy and carcinoids, either sporadic or as part of the spectrum of multiple endocrine neoplasias in adolescents, are among the few cases of ectopic ACTH that have been reported at the extremes of pediatric age. Ectopic ACTH caused by sarcomatous tumors is still rarer.[4,5] As far as we were able to determine, only 4 patients with ACTH-dependent Cushing syndrome caused by ES have been reported to date.[6–9]

We report the first case of ectopic ACTH with ES arising from the humerus. This case highlights this unique association and the morbidity associated with such dual presentations.

Abbreviations: ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone; ES, Ewing sarcoma.

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https://doi.org/10.1016/j.aace.2021.09.003

Case Report

A 9-year-old girl, a resident of Nepal, with an unremarkable medical history presented with complaints of facial puffiness with a flushed appearance and gradually increasing abdominal distension for the past 5 months. This was associated with progressive difficulty in getting up from the sitting position over the previous 2 months. One week before admission, low backache developed in her, and she became bedridden.

Clinical evaluation revealed generalized obesity with a height of −2 SDS, a weight of +1.5 SDS, and a body mass index of +2 SDS for her age. Her blood pressure was 130/80 mm Hg, which was above the 95th percentile for her age, thereby suggesting hypertension. Tanner staging was prepubertal for axillary, pubic hair, and breast development. There was mooning of the face, facial plethora, and acneiform eruptions over her forehead and cheeks along with the cervicodorsal fat pad. (Fig. 1) There was no hyperpigmentation, thinning of the skin, nevi, easy bruisability, or striae. Proximal muscle weakness was evident predominantly in the lower limbs. Spine tenderness was present over the dorsolumbar region, and there were no bony deformities.

Her serum cortisol level measured at 8 AM was 42 μg/dL (reference range for 8 AM serum cortisol, 4.3-22.4 μg/dL) with a cortisol level measured at 11 PM of 60 μg/dL (reference range, 3.09-16.66 μg/dL), suggesting a loss of circadian rhythm. Serum cortisol after the overnight dexamethasone suppression test (15 μg/kg/dose) was 60 μg/dL (reference value, <1.8 μg/dL), suggesting non-suppressibility. Serum cortisol was also not suppressible (ie, 45 μg/dL) to >50% from the baseline after the high-dose dexamethasone suppression test (120 μg/kg/d in 4 divided doses over 2 days). Her serum ACTH level was 225 pg/mL (reference range, 10-46 pg/mL). A magnetic resonance imaging scan of the brain with pituitary protocol-dynamic contrast enhancement revealed a normal shape and size of the pituitary gland. Chest x-ray showed a suspicious, lytic lesion in the proximal region of the left humerus (Fig. 2). Magnetic resonance imaging and 3-dimensional computed tomography scans of the left shoulder and humerus showed a heterogeneous mixed lytic and sclerotic lesion with a spiculated periosteal reaction with a multilobulated soft tissue lesion extending from the bone into the soft tissue surrounding the bone (Fig. 3). A computed tomography–guided tru-cut biopsy of the lesion and histopathologic examination revealed clusters of small round cells with individual cells showing scanty cytoplasm, small round nuclei with vesicular chromatin, and inconspicuous nucleoli with mitotic activity of 6/10 hpf to 8/10 hpf (Fig. 4). Findings of the CD99 immunostaining were positive and confirmed the presence of primitive neuroectodermal tumor/ES. Findings of the ACTH immunostaining using the horseradish peroxidase polymer detection system of the histopathologic sample were negative. Corticotropin-releasing hormone (CRH) immunostaining was not available at our

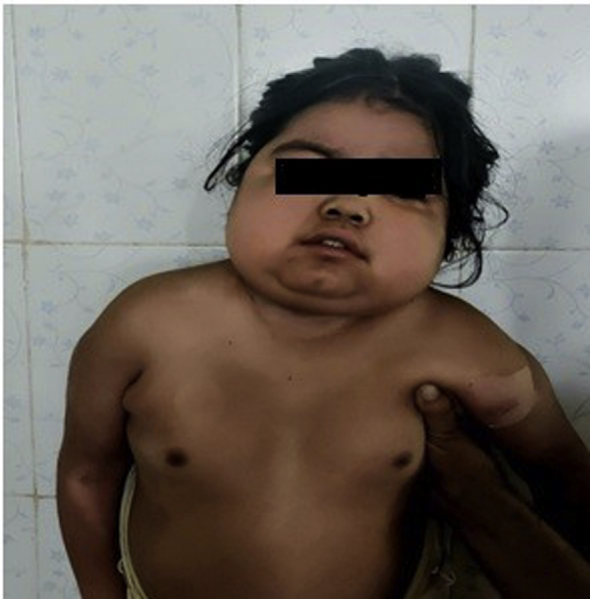

Fig. 1. Photograph of the patient showing mooning of the face and generalized obesity.

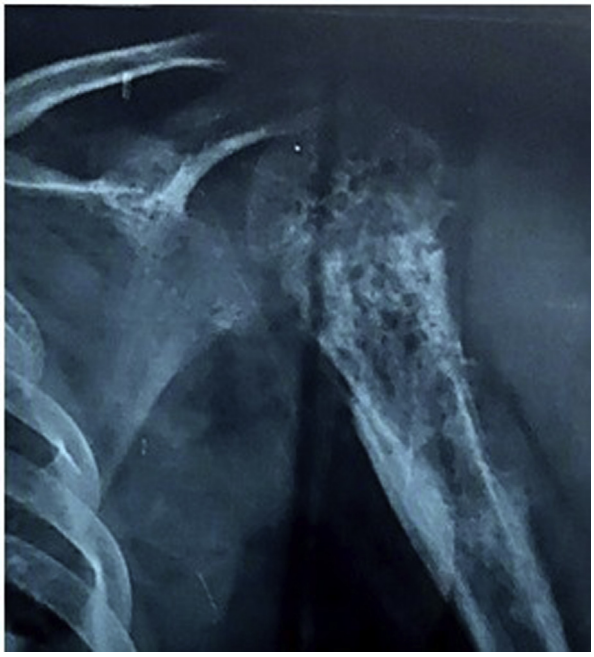

Fig. 2. An x-ray of the anterior-posterior view of the proximal aspect of the left humerus and shoulder showing a permeative lytic and sclerotic lesion.

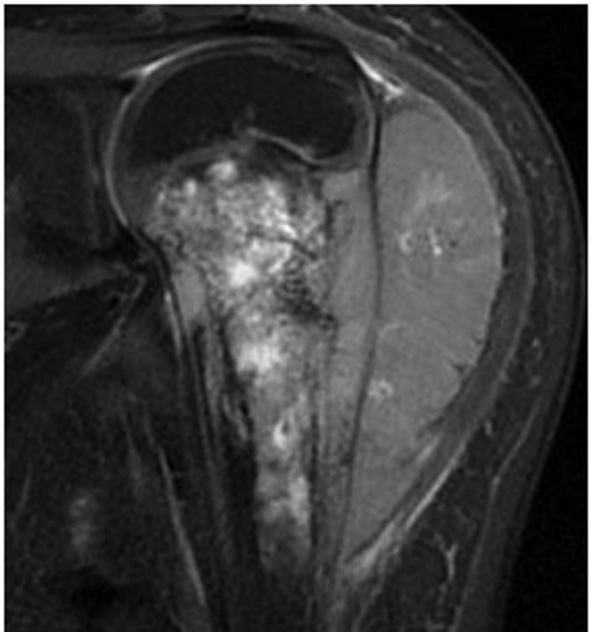

Fig. 3. T2 axial magnetic resonance imaging scan of the left shoulder and humerus showing a heterogeneous mixed lytic and sclerotic lesion with a spiculated periosteal reaction with a multilobulated soft tissue lesion.

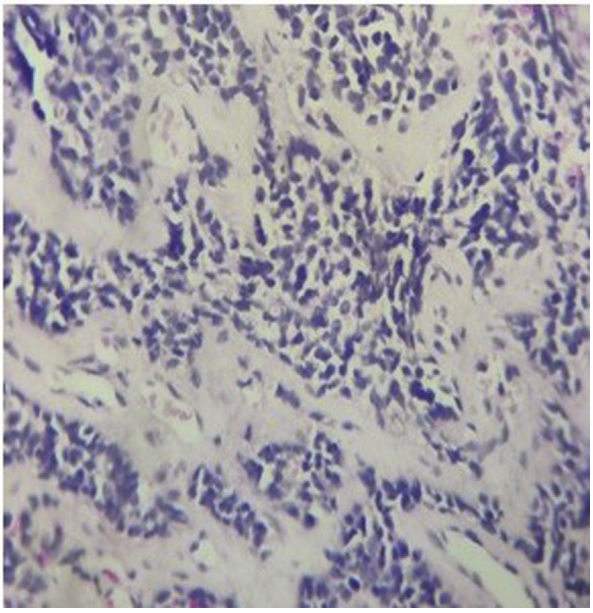

Fig. 4. Photomicrograph showing clusters of small round cells with individual cells showing scanty cytoplasm, small round nuclei with vesicular chromatin, and inconspicuous nucleoli. The stroma shows hyalinization and congested blood vessels. (Hematoxylin-eosin stain; *magnification*: x100.)

center. Computed tomography scans of the chest, abdomen, and pelvis with intravenous contrast were normal, and the computed tomography scan of the bone did not reveal any bone metastasis. Dorsolumbar spine x-ray revealed multiple wedge compression fractures involving T12-L2.

The child was treated with amlodipine and spironolactone for the control of hypertension and the correction of hypokalemia. She had persistent dysglycemia in the overt diabetes range with a fasting glucose level of 146 mg/dL and a postprandial glucose level of 250 mg/dL, for which insulin therapy was administered. Medical management of Cushing syndrome was started with ketoconazole at 400 mg/d in divided doses. A lumbar brace with assisted ambulation was provided for vertebral wedge compression fractures. The child was initiated on a chemotherapeutic regimen of cyclophosphamide, vincristine, and adriamycin alternating with ifosfamide and etoposide. Intravenous zoledronic acid 4 mg was administered for osteoporosis management. Seven days after chemotherapy, she succumbed to her illness. The medical issues were intractable vomiting and aspiration at the time of her death.

Discussion

Herein, we described the case of a 9-year-old girl with ectopic ACTH that appeared to have been due to ES involving the left humerus.

ES is a rare malignancy, involving the flat and long bones with a 5-year survival rate of 61%.[1] Approximately 10% to 15% of ACTH-dependent Cushing syndrome cases are due to ectopic ACTH. It is classically described in adults with small cell cancers of the lung, pancreatic neuroendocrine tumors, and bronchial carcinoids.[10] In children, ectopic ACTH is much rarer, and an extensive literature search by More et al[11] identified 48 cases with pancreatic neuroendocrine tumors and bronchial carcinoids predominantly.

The present case with ES and ectopic ACTH is based on nonsuppressibility of serum cortisol with the high-dose dexamethasone suppression test, normal pituitary on imaging, and severity of clinical features. However, findings of the ACTH immunostaining were negative. Possible explanations include the following: (1) the heterogeneous nature of malignant cells might have resulted in the areas examined not containing positive staining cells, (2) rapid secretion of ACTH might have exhausted the hormone stores that could be stained, and (3) antibodies used for immunohistochemistry may not identify the high molecular weight ACTH precursors or small ACTH-derived peptides.[12] CRH immunostaining was not performed as it was unavailable at our center. Ectopic secretion of CRH by nonhypothalamic tumors is <1%, and most cases are caused by neuroendocrine tumors of the lung, pancreas, or thymus. An extensive literature search by Shahani et al[13] revealed only 20 reported cases of ectopic CRH. Karageorgiadis et al[14] identified 7 patients with ACTH/CRH cosecreting tumors in a retrospective study spanning over 5 years with tumors localized to the pancreas, thymus, and liver. An argument could be made that our patient could have been secreting CRH, and it would have been identified had CRH staining been accessible; however, because of a normal-sized pituitary gland, this possibility appears remote. An inferior petrosal sinus sampling would have been more diagnostic in ruling out a pituitary source of ACTH excess but was not performed in this patient as her general condition did not permit the same. Additionally, serum dexamethasone levels, useful in the presence of malabsorption, interfering drugs, or noncompliance, help in the interpretation of suppression tests; however, as the patient was not on any other medications and the compliance was ensured as it was under direct observation, we did not perform the estimation of serum dexamethasone levels.

Given its rarity, ES presenting as ectopic ACTH has remained poorly described in the literature, and to our knowledge, this is the first case report of ES arising from the humerus presenting with ectopic ACTH. As far as we were able to determine, only 4 cases of ES presenting with ectopic ACTH have been described, and the present case is the first pediatric case reported from the Indian subcontinent.

The earliest report of ES leading to Cushing syndrome was described in a 12-year-old girl from Thailand with CRH secretion from the tumor in the tibia managed surgically with the resolution of symptoms.[6] Another case report from Turkey described a 9-year-old girl with features of Cushing syndrome with a retroperitoneal mass with histopathologically confirmed ES that was managed successfully with chemotherapy as surgical resection was not possible.[7] The third case was of a 20-year-old man from Switzerland with ES of the ribs, managed with surgical resection and chemotherapy but later on relapsed with pulmonary and costal lesions with Cushing syndrome. He was managed medically but succumbed to the illness on follow-up.[8] The fourth case was of a 10-year-old boy from Italy with Cushing syndrome caused by ectopic ACTH production from a metastatic ES tumor of the right ischiopubic rami with multiple secondaries who was managed with chemotherapy but succumbed to the illness.[9] The present case assumes significance in view of being the first case of ES of the humerus with ectopic ACTH.

The complete lack of local symptoms of the lesion and the extremely rapid lethal progression of ectopic ACTH are peculiar to this case. The previous cases described above did have local symptoms. The average duration of symptoms before a diagnosis of Cushing disease is approximately 2.5 years in children, whereas in cases of pediatric ectopic ACTH, there is a paucity of literature to derive a mean length.[15] In the present case, the symptomatology occurred 5 months prior to diagnosis. The hallmark of Cushing syndrome in childhood is the deceleration of growth velocity and associated unabated weight gain. Clinical features of ectopic ACTH vary in comparison to those of classic Cushing syndrome with a more rapid progression due to the nature of the underlying neoplasm and probably the reason for the patient in the present

case having no significant growth retardation or hyperpigmentation. Ectopic ACTH, in view of severe hypercortisolemia, has a prominent dysglycemia, edema, and hypokalemia, with the latter particularly suggestive of ectopic ACTH.[16] The patient in the present case had dysglycemia and hypokalemia.

Approximately 70% of patients with localized disease survive >5 years. Despite the patient in the present case having a localized disease, the comorbidities associated with ectopic ACTH and the simultaneous presence of an aggressive tumor led to an ominous outcome.

Conclusion

We report this case of ES associated with ectopic ACTH and the only presentation arising from the humerus. Managing the dual pathologies with advanced disease is complex, and further research into such rare presentations will help in the prompt identification of the disease and the administration of appropriate therapy, resulting in the best possible outcomes.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Cotterill SJ, Ahrens S, Paulussen M, et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study Group. *J Clin Oncol*. 2000;18(17):3108–3114.
2. Mirra JM, Picci P, Gold RH. *Bone Tumors: Clinical, Pathologic, and Radiologic Correlations*. Lea & Febiger; 1989:226–248.
3. Stratakis CA. Cushing syndrome in pediatrics. *Endocrinol Metab Clin North Am*. 2012;41(4):793–803.
4. Hsiao JC, Yang CP, Lin CJ, Chuen H. Ectopic ACTH syndrome due to clear cell sarcoma of the kidney. *Child Nephrol Urol*. 1991;11(2):103–106.
5. Hinnie J, Gray CE, McNicol AM, et al. Cushing's syndrome in a 16 year old girl due to ectopic ACTH precursor production from a pancreatic tumour. *Clin Endocrinol (Oxf)*. 2000;53(4):539–540.
6. Preeyasombat C, Sirikulchayanonta V, Mahachokelertwattana P, Sriphrapradang A, Boonpucknavig S. Cushing's syndrome caused by Ewing's sarcoma secreting corticotropin releasing factor-like peptide. *Am J Dis Child*. 1992;146(9):1103–1105.
7. Guran T, Turan S, Ozkan B, et al. Cushing's syndrome due to a non-adrenal ectopic adrenocorticotropin-secreting Ewing's sarcoma in a child. *J Pediatr Endocrinol Metab*. 2009;22(4):363–368.
8. Galland-Decker C, Kraege V, Sartori C. Central nervous system manifestations due to iatrogenic adrenal insufficiency in a Ewing sarcoma patient. *World J Emerg Med*. 2019;10(2):119–121.
9. Di Ruscio V, Del Baldo G, De Pasquale MD, et al. Ectopic ACTH secretion in a child with metastatic Ewing's sarcoma: a case report. *Front Oncol*. 2020;10:574.
10. Hernandez I, Espinosa-de-los-Monteros AL, Mendoza V, et al. Ectopic ACTH-secreting syndrome: a single center experience report with a high prevalence of occult tumor. *Arch Med Res*. 2006;37(8):976–980.
11. More J, Young J, Reznik Y, et al. Ectopic ACTH syndrome in children and adolescents. *J Clin Endocrinol Metab*. 2011;96(5):1213–1222.
12. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. *Endocr Rev*. 1998;19(5):647–672.
13. Shahani S, Nudelman RJ, Nalini R, Kim HS, Samson SL. Ectopic corticotropin-releasing hormone (CRH) syndrome from metastatic small cell carcinoma: a case report and review of the literature. *Diagn Pathol*. 2010;5(1):56.
14. Karageorgiadis AS, Papadakis GZ, Biro J, et al. Ectopic adrenocorticotropic hormone and corticotropin-releasing hormone co-secreting tumors in children and adolescents causing Cushing syndrome: a diagnostic dilemma and how to solve it. *J Clin Endocrinol Metab*. 2015;100(1):141–148.
15. Savage MO, Storr HL. Pediatric Cushing's disease: management issues. *Indian J Endocrinol Metab*. 2012;16(suppl 2):S171–S175.
16. Coates PJ, Doniach I, Howlett TA, Rees LH, Besser GM. Immunocytochemical study of 18 tumours causing ectopic Cushing's syndrome. *J Clin Pathol*. 1986;39(9):955–960.