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# Primitive neuroectodermal adrenal gland tumour

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## ABSTRACT

Ewing's sarcoma, also called primitive neuroectodermal tumour of the adrenal gland, is extremely rare. Only a few cases have been reported in the literature. We report on a woman with adult-onset primitive neuroectodermal tumour of the adrenal gland presenting with progressive flank pain. Computed tomography confirmed an adrenal tumour with invasion of the left diaphragm and kidney. Radical surgery was performed and the pain completely resolved; histology confirmed the presence of primitive neuroectodermal tumour, for which she was given chemotherapy. The clinical presentation of this condition is non-specific, and a definitive diagnosis is based on a combination of histology, as well as immunohistochemical and cytogenic analysis. According to the literature, these tumours demonstrate rapid growth and aggressive behaviour but there are no well-established guidelines or treatment strategies. Nevertheless,

surgery remains the mainstay of local disease control; curative surgery can be performed in most patients. Adjuvant chemoradiation has been advocated yet no consensus is available. The prognosis of patients with primitive neuroectodermal tumours remains poor.

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## Introduction

Ewing's sarcoma (ES), also called primitive neuroectodermal tumours (PNET), is a rare cancer of presumed neuroectodermal origin and is mostly found in children and young adults.<sup>1</sup> Since it usually involves the diaphysis of long bones, adrenal ES/PNET is extremely rare. To our knowledge, only a handful of cases have been reported in the literature. Herein we present a patient with adult-onset adrenal PNET and discuss the diagnostic and management issues.

## Case report

A 37-year-old woman presented to our hospital in May 2013 with progressive pain over left flank

and abdomen for 1 month. Physical examination revealed a ballotable mass over the left flank. Contrast computed tomography (CT) demonstrated a 12-cm left adrenal mass with infiltration to the left crus of diaphragm and upper pole of the left kidney (Fig). On closer examination, the left renal artery was encased by the tumour but there was no evidence of distant metastases. Hormonal workup of this adrenal mass suggested that it was a non-functioning tumour. There was no excess in 24-hour urinary catecholamines and metanephrines, while 24-hour urinary free cortisol excretion was 71 (reference range [RR], 24-140) nmol. The aldosterone-renin ratio was 9.0 (reference level, <20) ng/dL per ng/(mL•h). Luteinising hormone, follicle-stimulating hormone, and testosterone levels were 3.0 (RR, 1.2-103.0) IU/L, 6.8 (1.8-22.5) IU/L, and 0.83 (0.35-2.60) nmol/L, respectively. The dehydroepiandrosterone level was 4.5 (RR, 2-11)  $\mu$ mol/L. Owing to increasing pain and the rapidly growing tumour, she underwent surgery, which revealed a 12-cm adrenal tumour compressing the aorta and superior mesenteric artery, and the posterior part of the diaphragm and left renal artery were invaded by the tumour bulk. Accordingly, she underwent a left adrenalectomy together with radical nephrectomy and partial resection of the diaphragm. No gross tumour was left behind. Thereafter, she made a good uneventful recovery and was discharged on the fifth day. Her back pain resolved completely after surgery.

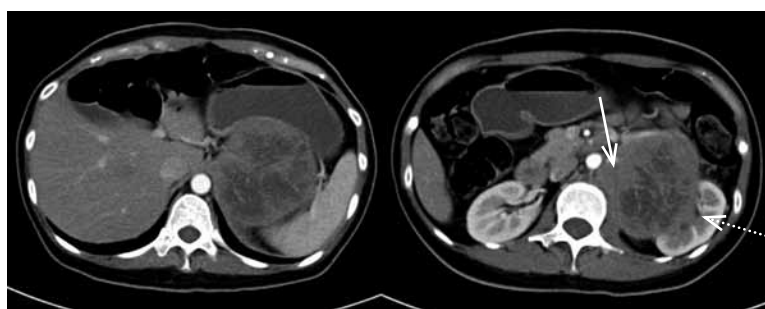


FIG. Left adrenal tumour with infiltration to the left diaphragmatic crus (solid arrow) and the left kidney (dotted arrow)

Histology revealed a monotonous population of small round tumour cells with hyperchromatic nuclei, small nucleoli, and minimal cytoplasm arranged in sheets and cords with occasional vague rosette formation. Karyorrhexis, mitosis, and 'starry sky' pattern were focally observed. Immunohistochemically, the tumour cells stained positively for MIC2 antigen (CD99), vimentin, and FLI1. By contrast they stained negatively for cytokeratin, leukocyte common antigen, MPO, WT1, synaptophysin, S100, desmin, myogenin, CD68, and CD34. The reverse transcriptase–polymerase chain reaction confirmed a reciprocal translocation of t(11;22)(q24;q12) involving the *EWSR1* gene on chromosome 22 and the *FLI1* gene on chromosome 11 (ie *EWSR1-FLI1* translocation). Overall, these findings were consistent with ES/PNET.

She received adjuvant chemotherapy (cyclophosphamide, adriamycin, and vincristine alternating with ifosfamide and etoposide). The latest CT at 5 months post-surgery revealed no evidence of local or distant recurrence.

## Discussion

Ewing's sarcoma/PNET of the adrenal gland is rarely

## 腎上腺原始神經外胚層腫瘤

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尤文氏肉瘤 (Ewing's sarcoma) 又稱為腎上腺原始神經外胚層腫瘤。這類腫瘤極為罕見，文獻中只記載了數個病例。本文報告一名女性患有成年始發的腎上腺原始神經外胚層腫瘤並出現持續加劇的腰痛。電腦斷層掃描證實其腎上腺腫瘤侵襲左側膈肌和腎臟。病人接受根治性手術後，痛楚完全消失，其後接受化療。組織學證實為原始神經外胚層腫瘤。尤文氏肉瘤沒有特定的臨床表現，所以往往要結合組織學、免疫組織化學和細胞遺傳學的分析才可為病人確診。據文獻報導，這類腫瘤的生長速度快，侵襲性強，可惜沒有行之有效的指引或治療策略。手術仍是主要治療方法，大部份患者均可接受治療性手術。雖然有人提倡輔助性放射性化療，但對此尚未達成共識。原始神經外胚層腫瘤患者的預後仍然欠佳。

reported.<sup>2,3</sup> Our review of the English literature revealed only 10 reports describing 16 patients (Table).<sup>3-12</sup> As in our patient, CD99, a highly sensitive marker for PNET, was found in all 16 of these patients. Although not routinely looked for, as in our patient over 90% of PNET cases exhibit a reciprocal translocation of t(11;22)(q24;q12) involving the

TABLE. Summary of case reports regarding clinical conditions<sup>3-12</sup>

Study	Sex/age (years)	Tumour size (cm)	Clinical features	Surgical resection*	CD99	Translocation of t(11;22)(q24;q12)	Adjuvant chemo (agent)*	RT	Outcome
Renshaw et al, <sup>3</sup> 1996	F/46 F/20 F/48	N/A	N/A	N/A	+	+	N/A	N/A	N/A
Matsuoka et al, <sup>6</sup> 1999	F/32	10	Pain	+ (R0)	+	N/A	+ (2 cycles) (IE / cisplatin)	-	Dead at 5 months after surgery (local recurrence and metastasis)
Pirani et al, <sup>7</sup> 2000	M/57	15	DVT	+ (R0)	+	+	N/A	N/A	N/A
Komatsu et al, <sup>8</sup> 2006	F/53	3	Nil	+ (R0)	+	N/A	-	-	Alive at 10 months after surgery (no metastasis or relapse)
Ahmed et al, <sup>9</sup> 2006	F/28	10	N/A	+ (R0)	+	+	+ (6 cycles) (agents N/A)	-	N/A
Kim et al, <sup>10</sup> 2006	F/24 F/25	8 15	Pain Pain	N/A	+	+	N/A	N/A	N/A
Lena, <sup>12</sup> 2009	F/74	16	N/A	+ (R1/R0†)	+	N/A	-	+ (palliative) (60 Gy)	Alive at 8 years after surgery and RT (local recurrence and metastasis)
Zhang and Li, <sup>4</sup> 2010	M/30 F/21 F/24 M/22	12 10 9 17	Pain / upon routine screening	+ (R2) - + (R0) + (R0)	+	N/A	- - + (12 cycles) (agent N/A) + (agent / cycles N/A)	+ (palliative) - - -	Dead at 8 months after surgery Dead at 6 months after diagnosis (metastasis) Alive at 13 months after surgery (metastasis) Alive at 1 month after surgery (local recurrence)
Yamamoto et al, <sup>5</sup> 2013	M/26	8	Nil	-	+	N/A	-	-	Dead (tumour found during autopsy)
Abi-Raad et al, <sup>11</sup> 2013	F/26	11	Pain	+ (R1)	+	+	+ (IE / VAC)	+ (adjuvant)	Alive at 8 months after surgery (no metastasis or relapse)

Abbreviations: chemo = chemotherapy; DVT = deep vein thrombosis; IE = ifosfamide and etoposide; N/A = data not available or not reported; RT = radiotherapy; VAC = vincristine, doxorubicin and cyclophosphamide

\* All surgeries were curative intent and all chemotherapies were adjuvant intent

† The patient had R1 resection of the adrenal tumour and refused chemo- and radio-therapies initially. She had local recurrence subsequently with reoperation and R0 resection. She had local relapse again and received radiotherapy afterwards

*EWSR1* gene on chromosome 22 and the *FLI1* gene on chromosome 11.<sup>1,3,6-9,11,12</sup> These 16 reported cases had a median age at diagnosis of 26 (range, 20-74) years, and the female-to-male ratio was 3:1. The median tumour size was 10.5 (range, 3-17) cm.

Nine of these patients underwent curative surgery despite rapid growth and aggressive tumour behaviour.<sup>4,7,8,12,13</sup> Nevertheless, in a few patients the tumour behaves indolently or has a relatively quiescent period before rapid growth. A case of incidental PNET at autopsy has been reported in a 26-year-old man who committed suicide by hanging himself; his latent PNET measured 8 cm.<sup>5</sup> Similarly, another patient aged 53 years underwent a laparoscopic adrenalectomy for a presumed non-functional incidental adrenocortical adenoma, but turned out to be a 3-cm PNET.<sup>8</sup>

### Diagnostic issues

It is difficult to make a definitive diagnosis of ES/PNET before surgery because currently it is based on a combination of histology, immunohistochemistry, and cytogenetic analysis.<sup>4,8</sup> Although needle biopsy is a possible approach to making a definitive diagnosis without resection, it is rarely performed unless the tumour is considered not resectable or adrenal metastases are suspected. Since our patient had a potentially resectable tumour with no evidence of distant metastases, needle biopsy was not considered. Furthermore, she was clearly suffering pain arising from the tumour and therefore surgical resection was clearly indicated.

### Management issues

Due to its rarity, there are no well-established guidelines or treatment strategies for PNET. Surgical resection remains the mainstay for local disease control.<sup>4,7,8</sup> Since the tumour is believed to be both chemo- and radio-sensitive, adjuvant chemotherapy and radiotherapy have often been advocated for better local and distant control, but there is no consensus.<sup>13</sup> A standard regimen of chemoradiation is not yet established due to the sporadic nature of cases.<sup>13</sup> Most chemotherapy regimens for adult-onset PNET are akin to those for ES in children as both share the same origin.<sup>4,14</sup> Chemotherapeutic agents such as cyclophosphamide, adriamycin, vincristine, ifosfamide, or etoposide have been used.<sup>4,7,8</sup> Recently, it has been noted that chemotherapy might be effective only for the first few cycles, and that the tumours develop resistance very quickly.<sup>4</sup> Adjuvant radiotherapy had been used for local recurrences as well as unresectable or incompletely resected PNETs.<sup>4,12</sup> From our review, adrenalectomies were performed for 11 patients, while chemotherapy and radiotherapy was also given to six and three of them, respectively. Follow-up revealed that these tumours were aggressive; three of the 16 patients

died within 1 year of diagnosis or surgery. Regarding the six patients who were still surviving when this report was submitted, one had distant metastasis and another two had local recurrence. Because of this high rate of recurrence, intensive follow-up with regular CT scans (every 6 months) has been advocated even after seemingly curative surgery.<sup>12</sup>

## Conclusion

Herein we report a rare case of adult adrenal PNET. The clinical presentation is often vague and non-specific and a definitive diagnosis depends on a combination of histology, immunohistochemistry, and cytogenetic analysis. Surgical resection remains the mainstay of treatment coupled with adjuvant chemoradiation. Nevertheless, the prognosis appears poor.

## References

- Grier HE. The Ewing family of tumors. Ewing's sarcoma and primitive neuroectodermal tumors. *Pediatr Clin North Am* 1997;44:991-1004.
- Quezado M, Benjamin DR, Tsokos M. EWS/FLI-1 fusion transcripts in three peripheral primitive neuroectodermal tumors of the kidney. *Hum Pathol* 1997;28:767-71.
- Renshaw AA, Perez-Atayde AR, Fletcher JA, Granter SR. Cytology of typical and atypical Ewing's sarcoma/PNET. *Am J Clin Pathol* 1996;106:620-4.
- Zhang Y, Li H. Primitive neuroectodermal tumors of adrenal gland. *Jpn J Clin Oncol* 2010;40:800-4.
- Yamamoto T, Takasu K, Emoto Y, et al. Latent adrenal Ewing sarcoma family of tumors: a case report. *Leg Med (Tokyo)* 2013;15:96-8.
- Matsuoka Y, Fujii Y, Akashi T, Gosehi N, Kihara K. Primitive neuroectodermal tumour of the adrenal gland. *BJU Int* 1999;83:515-6.
- Pirani JE, Woolums CS, Dishop MK, Herman JR. Primitive neuroectodermal tumor of the adrenal gland. *J Urol* 2000;163:1855-6.
- Komatsu S, Watanabe R, Naito M, et al. Primitive neuroectodermal tumor of the adrenal gland. *Int J Urol* 2006;13:606-7.
- Ahmed AA, Nava VE, Pham T, et al. Ewing sarcoma family of tumors in unusual sites: confirmation by rt-PCR. *Pediatr Dev Pathol* 2006;9:488-95.
- Kim MS, Kim B, Park CS, et al. Radiologic findings of peripheral primitive neuroectodermal tumor arising in the retroperitoneum. *AJR Am J Roentgenol* 2006;186:1125-32.
- Abi-Raad R, Manetti GJ, Colberg JW, Hornick JL, Shah JG, Prasad ML. Ewing sarcoma / PNET arising in the adrenal gland. *Pathol Int* 2013;63:283-6.
- Lena M. Retroperitoneal primitive neuroectodermal tumour (PNET). A case report and review of the literature. *Rep Practical Oncol Radiother* 2009;14:221-4.
- Malpica A, Moran CA. Primitive neuroectodermal tumor of the cervix: a clinicopathologic and immunohistochemical study of two cases. *Ann Diagn Pathol* 2002;6:281-7.
- Bisogno G, Carli M, Stevens M, et al. Intensive chemotherapy for children and young adults with metastatic primitive neuroectodermal tumors of the soft tissue. *Bone Marrow Transplant* 2002;30:297-302.