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CASE REPORT

PEComa of the terminal ileum mesentery as a secondary tumour in an adult survivor of embryonal rhabdomyosarcoma

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ABSTRACT

Perivascular epithelioid cell tumours (PEComas) are rare mesenchymal tumours that are characterized by perivascular epithelioid cell differentiation and immunoreactivity to myogenic and melanocytic markers. These tumours can be classified as benign, uncertain malignant potential, or malignant. Because of the rarity of PEComas, their cause and clinical prognosis remain unclear.

To the best of our knowledge, no reports in the literature describe a PEComa of the terminal ileum mesentery as a secondary tumour in an adult survivor of childhood embryonal rhabdomyosarcoma, let alone any childhood cancer. Here, we present the case of a 27-year-old man with a PEComa involving the mesentery of the terminal ileum. At the age of 5, he had been treated with a combination of chemotherapy and high-dose pelvic radiation therapy for embryonal rhabdomyosarcoma, most likely arising from the posterior bladder wall.

During routine follow-up 22 years after this patient's initial treatment, computed tomography imaging revealed a mass within the terminal ileum mesentery. The tumour was successfully treated with surgical resection, and pathology examination determined the mass to be a PEComa with uncertain malignant potential.

This first case of a PEComa of the terminal ileum mesentery arising within a high-dose radiation therapy field as a secondary tumour in an adult survivor of childhood cancer highlights the importance of screening and surveillance in high-risk childhood cancer survivors treated with high-dose radiation therapy. Further research to build a better understanding of this remarkably rare tumour is warranted.

Key Words PEComa, terminal ileum mesentery, secondary neoplasms, rhabdomyosarcoma, childhood cancer, radiation therapy

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INTRODUCTION

Although multimodal therapy has resulted in improved long-term survival for children diagnosed with rhabdomyosarcoma, childhood rhabdomyosarcoma survivors are at an increased risk of developing secondary neoplasms[1]. The 10-year cumulative incidence rate for development of a secondary neoplasm is 1.7%, with median time to onset being 7 years and the most common secondary neoplasm being bone sarcoma[2]. The risk in these cases is attributable primarily to the initial cancer treatment, with a higher risk being observed in children treated with a combination of high-dose radiation therapy (RT) and chemotherapy, young age at diagnosis, and a genetic predisposition to cancer[1–3]. Although secondary neoplasms arising in a high-dose RT field are a well-known complication of childhood cancer[3], the present report concerns the first case of a perivascular epithelioid cell tumour (PEComa) of the terminal ileum mesentery arising 22 years after treatment as a secondary neoplasm within a high-dose RT field in an adult survivor of embryonal rhabdomyosarcoma.

Perivascular epithelioid cell tumours belong to a group of rare mesenchymal soft-tissue tumours that consist of perivascular epitheloid cells and that can be classified as benign, uncertain malignant potential, or malignant[4–6]. Almost all have immunoreactivity to myogenic (actin or desmin, or both) and melanocytic (HMB-45 or Melan-A, or both) markers[7]. These tumours arise mostly in adults at visceral, retroperitoneal, and abdominopelvic sites[8].

Because of the rarity of PEComas, their cause remains for the most part unknown. Perivascular epithelioid cell tumours of the mesentery are remarkably rare, and fewer

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than 10 cases are currently reported in the literature[4,9–12]. To the best of our knowledge, the literature current contains no reports describing a PEComa of the terminal ileum mesentery as a secondary tumour in a survivor of childhood cancer. Our case highlights the importance of screening and surveillance in high-risk childhood cancer survivors treated with high-dose radiation therapy. Further research to improve the understanding of this remarkably rare tumour is warranted.

CASE PRESENTATION

A 27-year-old man had been treated at age 5 for an embryonal rhabdomyosarcoma of the prostate and posterior bladder wall. He received chemotherapy (doxorubicin to a total dose 343 mg/m^2, vincristine, cyclophosphamide, cisplatin, and actinomycin D) plus pelvic RT by the parallel opposed-pair technique to 50 Gy in 25 fractions. He developed hemorrhagic cystitis as an early complication of the cyclophosphamide and pelvic RT, which resolved completely. Late complications of therapy included bilateral hydroceles (treated surgically), two stable echogenic liver lesions secondary to benign focal nodular hyperplasia, and urethral stricture requiring intermittent dilation. No evidence of recurrent rhabdomyosarcoma had ever been observed.

During routine follow-up, computed tomography (CT) imaging showed a new, 3.1×2.7×3.9 cm isodense mass with well-defined borders in the right lower quadrant adjacent to loops of the distal terminal ileum (Figure 1), within the patient's previous high-dose RT field. No radiologic signs of malignancy were observed other than the presence of the new isodense mass, and no evidence was seen of invasion of adjacent structures or enhancement. No pelvic abnormality was palpable on examination.

The patient had no clinical features of tuberous sclerosis complex and *TSC1/2* mutation testing was not performed because the patient declined genetic testing. He underwent resection of the mass, and the pathology was consistent with a PEComa. The margins of excision were negative. More than 3 years later, no evidence of recurrent PEComa has been observed.

Gross pathologic examination revealed a tumour nodule in the mesentery, with overlying intact serosa, 2 cm from the mesenteric resection margin. The nodule was well-circumscribed and rubbery in nature, with a brown-tan fleshy appearance on the cut surface. Histologically, the tumour was composed predominantly of large polygonal epithelioid cells with abundant clear-to-granular eosinophilic cytoplasm arranged in subtle nests surrounded by delicate capillary vessels [Figure 2(A)]. The tumour cells showed binucleate, and occasionally multinucleate, morphology. There was focal association with the walls of blood vessels. No necrosis was evident, and the mitotic rate was 2 in 50 high-power fields. Immunohistochemistry revealed that the tumour cells reacted diffusely to the melanocytic markers HMB-45 and Melan-A [Figure 2(B).]

Risk stratification in PEComa uses the classification system developed by Folpe *et al.*[4], which takes into account a number of high-risk histopathologic features (size > 5 cm, infiltrative growth pattern, high nuclear grade and cellularity, mitotic rate ≥ 1 in 50 high-power fields, necrosis, and vascular invasion) to stratify the tumours into "benign," "uncertain malignant potential," and "malignant" risk categories. The proposed criteria for PEComas exhibiting uncertain malignant potential consists of nuclear pleomorphism or multinucleated giant cells or tumour size exceeding 5 cm. Additionally, PEComas with only 1 high-risk histopathologic feature other than nuclear pleomorphism

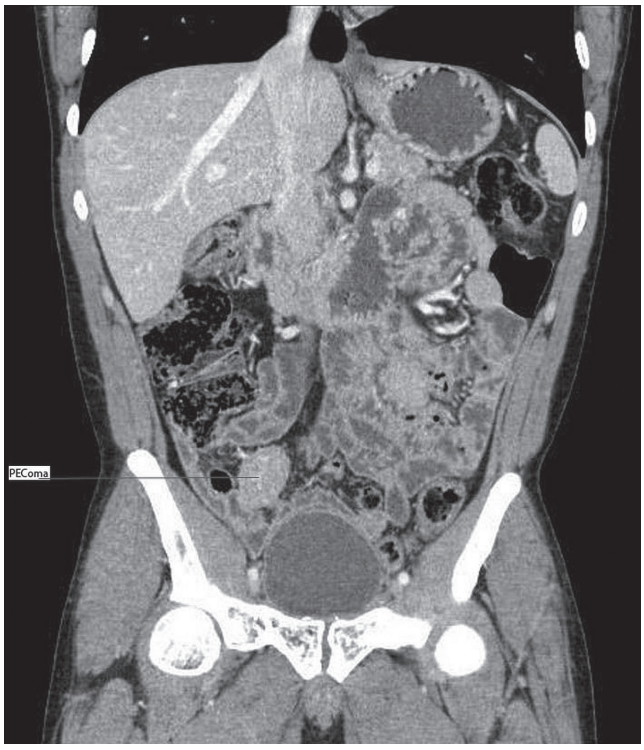

FIGURE 1 Computed tomography image shows a mass adjacent to the distal terminal ileum.

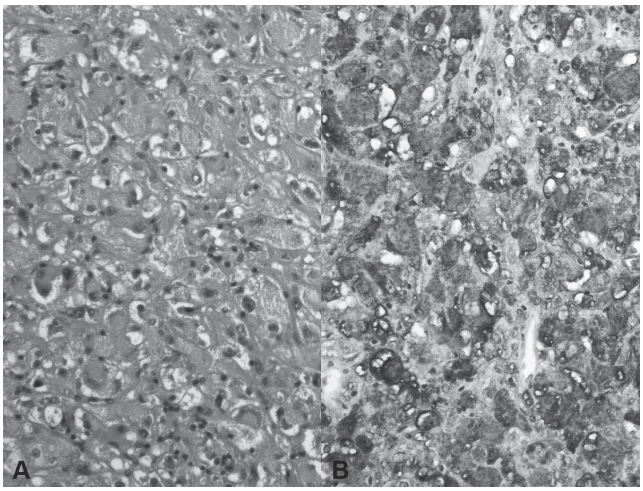

FIGURE 2 (A) Section shows large polygonal cells with ample eosinophilic granular cytoplasm. Hematoxylin and eosin stain, 20× magnification. (B) Section shows evident cytoplasmic positivity in tumour cells. HMB-45 stain (melanocytic marker), 20× magnification.

or multinucleated giant cells are categorized as "uncertain malignant potential." Based on that classification scheme, the presence of nuclear pleomorphism or multinucleated giant cells and a mitotic rate exceeding 1 in 50 high-power fields led to a final diagnosis of PEComa with uncertain malignant potential in this case. Nevertheless, classifying a PEComa as malignant on morphology grounds alone might not be highly accurate. Based on histologic characteristics, PEComas can be classified as benign, but can in fact have aggressive clinical behavior, with the opposite being true for malignant PEComas[13].

DISCUSSION

Most PEComas can be characterized by a distinct histology and immunohistochemistry profile. The epithelioid (in some cases, spindled) cells with clear-to-granular eosinophilic cytoplasm that make up PEComas show focal association with blood vessel walls and (generally) immunoreactivity to melanocytic (HMB-45 or Melan-A, or both) and myogenic (actin or desmin, or both) markers[7,8]. Imaging characteristics for PEComas vary considerably, and preoperative imaging alone is incapable of establishing a definitive diagnosis of PEComa. However, certain imaging characteristics can help to improve the diagnosis of PEComa[14]: low-density appearance on CT images, hypointense appearance on T1-weighted magnetic resonance imaging, and hyperintense appearance on T2-weighted imaging[14,15]. Furthermore, PEComas typically have well-defined borders and are heterogeneously enhanced in the arterial and venous phases[14,15].

Malignancy criteria for PEComas are not well established, which poses difficulty for predicting clinical behaviour[12,16]. This lack of criteria is primarily a result of the tumour's rarity and the limited follow-up reported in most cases[12,17,18]. The limited number of malignant cases published thus far have described malignant spread as being characterized by a locally infiltrative growth pattern, vascular invasion, a high mitotic rate, necrosis, and tumour size exceeding 8 cm[4,14,16,19–22]. The clinical behaviour of PEComas is generally benign. However, PEComas can display aggressive clinical behaviour, and some reported cases resulted in death[10,11].

Although PEComas can be found at various anatomic sites, they are markedly more frequent in women, with 40% developing in the gynecologic tract[4,8]. In particular, the ratio of PEComas of the mesentery by sex is 2:1 (women:men)[9]. Furthermore, in most case reports of PEComa of the mesentery, the tumour was malignant, with recurrence being reported within 6–22 months. However it should be noted that such recurrence could be attributed to a few cases being treated with a combination of chemotherapy and RT after surgical resection[9]. The mean survival time for a malignant PEComa of the terminal ileum is estimated to be 28 months[23].

Only two cases in the literature reported PEComa occurrence as a secondary tumour after treatment for childhood cancer. Honda *et al.*[24] described a PEComa (more specifically, a hepatic angiomyolipoma) occurring in a 19-year-old man 14 years after treatment for a stage IV pelvic rhabdomyosarcoma. This survivor had undergone 4 cycles of chemotherapy, pelvic exenteration, and intraoperative radiation with no evidence of recurrence. His PEComa was successfully treated with surgical resection, and immunohistochemistry showed that the tumour cells were positive for melanocytic marker HMB-45. Histology was characteristic of a PEComa. No evidence of recurrence was observed 8 months after treatment. Iyengar *et al.*[16] reported a PEComa of the orbit occurring in a 9-year-old girl 8 years after treatment for a perianal embryonal rhabdomyosarcoma. This survivor had undergone chemotherapy and surgery, and no recurrence had been evident. Her PEComa was also successfully treated with surgical resection. The immunohistochemistry profile showed positivity for the melanocytic marker HMB-45 and for the tyrosinase and myogenic markers calponin and smooth muscle actin. Histology was characteristic of a PEComa. No evidence of recurrence was seen at her 7-month follow-up. Both cases demonstrate the distinctive immunohistochemistry and histology associated with PEComas, as well as the extreme rarity of these tumours arising as secondary tumours in childhood cancer survivors.

Because of the difficulty in accurately predicting the behaviour of PEComas and the limited number of cases with long-term follow-up, a cautious clinical approach in which PEComas are regarded as tumours with uncertain malignant potential in the absence of malignant characteristics is recommended[16].

Treatment of PEComas can be quite complex. Surgery is often the best course of treatment because PEComas do not respond well to chemotherapy or RT[4–6]. Most importantly, routine follow-up after treatment is essential, and in our case, the patient has remained disease-free for more than 3 years.

The Children's Oncology Group Long-Term Follow-Up Guidelines state that physical examination, including inspection and palpation of skin and soft tissues exposed in the RT field, should be conducted annually to assess for a potential secondary benign or malignant neoplasm in childhood cancer survivors treated with RT[25]. However, no specific guidelines for secondary neoplasms in childhood cancers treated with pelvic RT have addressed the role of imaging in screening (for example, frequency or type of imaging). Long-term surveillance is an essential aspect of patient management because PEComa recurrences have been reported more than 5 years after treatment[26]. Based on our clinical expertise, we have scheduled our patient for and annual clinical examination consisting of magnetic resonance or CT imaging (depending on availability), to screen for secondary neoplasm or recurrence. Because of resource issues, magnetic resonance or CT imaging might not be accessible, and an alternative patient management strategy to screen for secondary neoplasms or recurrence is to conduct an annual clinical examination with ultrasonography and to evaluate the need for further imaging[27–29].

SUMMARY

Although development of a PEComa is a rare occurrence, our case illustrates the need for further research to determine the optimal use of imaging to screen for secondary

neoplasms after high-dose RT. It also highlights the importance of long-term follow-up for survivors of high-risk childhood cancers.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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REFERENCES

1. Scaradavou A, Heller G, Sklar CA, Ren L, Ghavimi F. Second malignant neoplasms in long-term survivors of childhood rhabdomyosarcoma. *Cancer* 1995;76:1860–7.
2. Heyn R, Haeberlen V, Newton WA, *et al.* Second malignant neoplasms in children treated for rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Committee. *J Clin Oncol* 1993;11:262–70.
3. Bhatia S, Sklar C. Second cancers in survivors of childhood cancer. *Nat Rev Cancer* 2002;2:124–32.
4. Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL, Weiss SW. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. *Am J Surg Pathol* 2005;29:1558–75.
5. Folpe AL, Kwiatkowski DJ. Perivascular epithelioid cell neoplasms: pathology and pathogenesis. *Hum Pathol* 2010;41:1–15.
6. Wu JH, Zhou JL, Cui Y, Jing QP, Shang L, Zhang JZ. Malignant perivascular epithelioid cell tumor of the retroperitoneum. *Int J Clin Exp Pathol* 2013;6:2251–6.
7. Martignoni G, Pea M, Reghellin D, Zamboni G, Bonetti F. PEComas: the past, the present and the future. *Virchows Arch* 2008;452:119–32.
8. Hornick JL, Fletcher CD. PEComa: what do we know so far? *Histopathology* 2006;48:75–82.
9. Fu X, Jiang JH, Gu X, Li Z. Malignant perivascular epithelioid cell tumor of mesentery with lymph node involvement: a case report and review of literature. *Diagn Pathol* 2013;8:60.
10. Gross E, Vernea F, Weintraub M, Koplewitz BZ. Perivascular epithelioid cell tumor of the ascending colon mesentery in a child: case report and review of the literature. *J Pediatr Surg* 2010;45:830–3.
11. Lai CL, Hsu KF, Yu JC, *et al.* Malignant perivascular epithelioid cell tumor of the mesentery: a case report and literature review. *Onkologie* 2012;35:114–17.
12. Agaimy A, Wunsch PH. Perivascular epithelioid cell sarcoma (malignant PEComa) of the ileum. *Pathology Res Pract* 2006;202:37–41.
13. de León DC, Pérez-Montiel D, Bandera A, Villegas C, Gonzalez-Conde E, Vilchis JC. Perivascular epithelioid cell tumor of abdominal origin. *Ann Diagn Pathol* 2010;14:173–7.
14. Khaja F, Carilli A, Baidas S, Sriharan A, Norford S. PEComa: a perivascular epithelioid cell tumor in the liver-a case report and review of the literature. *Case Rep Med* 2013;2013:904126.
15. Tan Y, Zhang H, Xiao EH. Perivascular epithelioid cell tumour: dynamic CT, MRI and clinicopathological characteristics—analysis of 32 cases and review of the literature. *Clin Radiol* 2013;68:555–61.
16. Iyengar P, Deangelis DD, Greenberg M, Taylor G. Perivascular epithelioid cell tumor of the orbit: a case report and review of the literature. *Pediatr Dev Pathol* 2005;8:98–104.
17. Vang R, Kempson RL. Perivascular epithelioid cell tumor ('PEComa') of the uterus: a subset of HMB-45–positive epithelioid mesenchymal neoplasms with an uncertain relationship to pure smooth muscle tumors. *Am J Surg Pathol* 2002;26:1–13.
18. Gronchi A, Diment J, Colecchia M, Fiore M, Santinami M. Atypical pleomorphic epithelioid angiomyolipoma localized to the pelvis: a case report and review of the literature. *Histopathology* 2004;44:292–5.
19. Pan CC, Yu IT, Yang AH, Chiang H. Clear cell myomelanocytic tumor of the urinary bladder. *Am J Surg Pathol* 2003;27:689–92.
20. Bonetti F, Martignoni G, Colato C, *et al.* Abdominopelvic sarcoma of perivascular epithelioid cells. Report of four cases in young women, one with tuberous sclerosis. *Mod Pathol* 2001;14:563–8.
21. Tazelaar HD, Batts KP, Srigley JR. Primary extrapulmonary sugar tumor (PEST): a report of four cases. *Mod Pathol* 2001;14:615–22.
22. Folpe AL, Goodman ZD, Ishak KG, *et al.* Clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres: a novel member of the perivascular epithelioid clear cell family of tumors with a predilection for children and young adults. *Am J Surg Pathol* 2000;24:1239–46.
23. Waters PS, Mitchell DP, Murphy R, McKenna M, Waldron RP. Primary malignant gastric PEComa—diagnostic and technical dilemmas. *Int J Surg Case Rep* 2012;3:89–91.
24. Honda M, Lee KJ, Hashimoto S, *et al.* Development of hepatic angiomyolipoma accompanied with focal nodular hyperplasia long after treatment of pelvic rhabdomyosarcoma. *J Pediatr Surg* 2011;46:1267–70.
25. Children's Oncology Group. *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.* Ver. 3.0. Arcadia, CA: Children's Oncology Group; 2008. [Current version downloadable from: http://www.survivorshipguidelines.org; cited 15 December 2013]
26. Bleeker J, Quevedo J, Folpe A. "Malignant" perivascular epithelioid cell neoplasm: risk stratification and treatment strategies. *Sarcoma* 2012;2012:541626.
27. Sanders RC, McNeil BJ, Finberg HJ, *et al.* A prospective study of computed tomography and ultrasound in the detection and staging of pelvic masses. *Radiology* 1983;146:439–42.
28. Grimer R, Judson I, Peake D, Seddon B. Guidelines for the management of soft tissue sarcomas. *Sarcoma* 2010;2010:506182.
29. Lakkaraju A, Sinha R, Garikipati R, Edward S, Robinson P. Ultrasound for initial evaluation and triage of clinically suspicious soft-tissue masses. *Clin Radiol* 2009;64:615–21.