CASE REPORT

Metachronous renal Ewing sarcoma/primitive neuroectodermal tumour in a survivor of Burkitt lymphoma

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SUMMARY

We present a case of a 14-year-old girl who was diagnosed with Burkitt lymphoma in 2014. She was managed with chemotherapy and remained in remission for 3 years. On her surveillance imaging in 2017, a left-sided renal neoplastic mass was incidentally discovered. She underwent nephrectomy and pathology of the resected specimen revealed small cell tumour of the kidney with features favouring renal Ewing sarcoma/primitive neuroectodermal tumour. Molecular genetic analysis by fluorescence in situ hybridisation was performed which showed translocation of 22q12, thereby confirming the diagnosis. This is a rare secondary malignancy and an unusual association. This case highlights the importance and diagnostic dilemmas of rare secondary tumours in patients with such haematological malignancies and discusses its possible pathogenetic aspects.

in such instances remains uncertain. Generally, non-random somatic molecular or chromosomal modifications are implicated in the development of secondary cancers.¹

Secondary malignancies are frequently found in those who have had a primary haematological malignancy in childhood. Surveillance of secondary malignancy may be especially important in patients with Burkitt lymphoma (BL) considering its high curability rate and the intensity of treatment; however, the exact rate of development of metachronous cancers in such patients is unknown. Recently, we diagnosed a case of renal Ewing sarcoma (ES)/primitive neuroectodermal tumour (PNET) that was incidentally discovered during regular surveillance imaging in a survivor of BL. This is an unusual occurrence and there have been no reported cases of metachronous renal ES/PNET in patients with such haematological malignancies.

BACKGROUND

The metachronous development of secondary malignancies of a different histological type and at a different location has always been a subject of concern in cancer survivors. Attributable factors include those linked to the tumour itself, genetic makeup of the patient, pre-existing conditions and most importantly therapy-related interventions. Most often, secondary malignancies can be linked to the long-lasting cytotoxic effects of radiotherapy, chemotherapy, immunotherapy and endocrine therapy. However, the exact underlying mechanism of tumorigenesis

CASE PRESENTATION

A 14-year-old girl presented with abdominal distension and abdominal pain in 2014. She had no significant medical or surgical history. She underwent a CT scan and was suspected to have a lymphoproliferative disorder with abdominal manifestations (ascites, omental thickening and nodularity) (figure 1). Ascitic fluid analysis, omental deposit histopathology and bone marrow biopsy along with immunochemical and genetic analysis confirmed the diagnosis of BL with positive t(8; 14) translocation. She was diagnosed as stage III and central nervous system negative, and treated based on FAB/LMB96 protocol with COP/

Figure 1 CT scan in 2014 showing gross ascites and extensive omental thickening with peritoneal nodularity. The diagnosis based on ascitic fluid analysis and omental and bone marrow biopsy along with immunochemistry and genetic analysis was Burkitt lymphoma.

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Table 1 Abbreviations key

BL	Burkitt lymphoma
ES	Ewing sarcoma
PNET	Primitive neuroectodermal tumour
CNS	Central nervous system
FAB/LMB96	French-American-British/Lymphomes Malins B 96 international study
COPADM	C=Cyclophosphamide O=Vincristine (Oncovin) P=Prednisolone A=Doxorubicin (Adriamycin) M=Methotrexate
CYM	CY=Cytarabine, M=Methotrexate
PAS+/-D	Periodic acid–Schiff–diastase
CD99 (MIC2)	Cluster of differentiation 99
BCL-2	B-cell lymphoma 2
EMA	Epithelial membrane antigen
WT1	Wilms tumor-1
FISH	Fluorescence in situ hybridisation
COG	Children's oncology group
VDC/IE	V=Vincristine D=Doxorubicin C=Cyclophosphamide I=Ifosfamide E=Etoposide
SRBCT	Small round blue cell tumour
EWSR1	Ewing sarcoma breakpoint region 1
ETS	Erythroblast transformation-specific
FLI1	Friend leukaemia integration 1 transcription factor
RT-PCR	Reverse transcription PCR

COPADM 1, 2 and CYM 1, 2 chemotherapy cycles (table 1) which included vincristine, methotrexate, doxorubicin and cyclophosphamide, and she went into complete remission within 3 months of therapy (figure 2).

Routine follow-up imaging in 2017 revealed a large heterogeneous neoplastic mass with areas of necrosis arising from the lower pole of the left kidney, measuring 7×6×8 cm (figure 3). There was no associated lymphadenopathy or metastatic disease. A left nephroureterectomy was done. Intraoperative findings showed a large tumour in the lower pole of the kidney. The mesocolon and descending colon were adherent over the tumour, but were separated. No peritoneal deposits or enlarged lymph nodes were found.

Figure 2 Within 3 months of high-intensity chemotherapy, there was complete remission of the disease.

INVESTIGATIONS

Histopathology revealed a solid, cystic, haemorrhagic renal lesion. Sections examined showed uniform population of small-to-intermediate-sized cells arranged in sheets and rosettes. The neoplastic cells had round to slightly irregular, hyperchromatic nuclei and scant cytoplasm. Intervening areas showed haemorrhagic spaces filled with blood. Special stain (PAS+/-D) highlighted focal cytoplasmic glycogen. Immunohistochemical stains were performed and the tumour cells showed strong, diffuse, membranous staining for CD99 (MIC 2) immunostains (figure 4). Tumour cells were also positive for cyclin D1 and BCL-2 immunostains. Cytokeratin AE1/AE3, EMA, desmin and WT1 were negative (table 1). The renal capsule and right ureter were tumour free. The final diagnosis was small round blue cell tumour (SRBCT) with features favouring renal ES/PNET. Molecular genetic analysis by fluorescence in situ hybridisation (FISH) was performed which showed translocation of 22q12, thereby confirming the diagnosis.

OUTCOME AND FOLLOW-UP

Postoperatively, the child remained stable. She has been started on chemotherapy based on the COG Ewing's protocol with alternating cycles of VDC/IE and is presently doing well.

DISCUSSION

BL is a subtype of non-Hodgkin's lymphoma with an incidence of about 0.4 cases per 100 000. BL is managed with recently updated high-intensity, short-duration combination chemotherapy. Treatment is most often curative with approximately 90% of paediatric patients obtaining long-term remission.² Therefore, development of a second malignancy in such survivors has always remained an important concern.³ The rate of development of secondary tumours can be as high as 21% according to previous reports and the latent period between the developments of two neoplasms is also variable.⁴ The most frequently reported secondary malignancies in this subset of patients include cancers of the head and neck, lung, colon, bladder, kidney, melanoma, thyroid, leukaemias and various sarcomas such as Kaposi sarcoma.⁵

The rate of secondary malignancies in patients with BL is unknown, and the probability is found to be higher in other forms of non-Hodgkin's lymphoma such as lymphoblastic lymphoma or large-cell lymphoma. There are only few reports on ES as a secondary malignancy and most reported cases comprise single case reports or series following therapy for leukaemias, Wilms tumour (WT), neuroblastoma, retinoblastoma or germ cell tumours. These secondary ES tumours have primarily involved

Figure 3 Surveillance CT imaging in 2017 revealing a large heterogeneous neoplastic lesion with areas of necrosis arising from the lower pole of left kidney. There was no lymphadenopathy or metastatic disease. This proved to be renal Ewing sarcoma/primitive neuroectodermal tumour on pathology.

Figure 4 (A) The renal lesion was composed of uniform population of basophilic cells arranged in sheets and rosettes. (B) The neoplastic cells had round to slightly irregular, hyperchromatic nuclei and scant cytoplasm. (C) Immunohistochemical stains were performed which showed positive CD99.

sites such as the ribs, chest wall, soft tissues, pelvis and extremities and do not appear to be related to radiotherapy.^{6–9} An unusual case of ES of the adrenal gland is the only documented case of secondary ES in a survivor of BL.¹⁰ Renal ES/PNET is an extremely rare and aggressive SRBCT, affecting adolescents and young adults. This tumour has an incidence of about 1 in 1 000 000 with a male to female ratio of 1.5:1. Less than 100 cases have been reported to date globally.¹¹

Cytogenetic features of renal ES/PNET include fusion of the EWSR1 gene with a member of the ETS family of oncogenes, arising at a specific chromosomal translocation. More than 90% of these are reciprocal translocations $t(11;22)(q24;q12)$, resulting in an EWSR1/FLI1 fusion transcript.¹² In ES as a secondary malignancy, it is advocated that antitumour activity of the innate or adaptive immune system may get impaired, therefore causing dysfunction and inability of the system to identify and eradicate the newly mutated cells carrying the ES translocation, therefore initiating the development of secondary ES.¹ Our patient received intensive chemotherapy for BL and because of the relatively short latent period of occurrence of this malignancy (3 years), the previous exposure to doxorubicin might be implicated with development of secondary ES. This is because topoisomerase II inhibitor-associated secondary malignancies have relatively shorter latent periods than those associated with alkylating agents.¹⁰

Histologically, it can be challenging to differentiate renal ES from other SRBCTs, synovial sarcoma, malignant lymphoma, WT, neuroblastoma and small cell neuroendocrine tumour because these tumours often show overlapping cytomorphological features.¹³ Therefore, immunocytochemistry and detection of the translocation by FISH or RT-PCR

techniques have always been critical in reaching the diagnosis. The basis of diagnosis of our case as renal ES/PNET were histomorphology of SRBCT, immunohistochemical positivity of CD99 and presence of EWSR1 gene rearrangement. This molecular signature is typical for the PNET as well. In the current WHO classification, PNET which was once believed to be a separate disease is now included as part of the histological spectrum of the ‘Ewing family of tumours’.¹⁴

The radiographic features of renal ES/PNET are non-specific and almost indistinguishable from renal cell carcinoma.

Learning points

- It is vital to understand the potential of development of secondary malignancies, both treatment-related and associated with the genetic background of patients with cancer because their survival will continue to improve in the near future due to substantial improvements in multimodal therapy regimens.
- It is essential to distinguish primary renal Ewing sarcoma from the other small blue round cell tumours by immunohistochemical and genetic methods because radiological and histological features often overlap, and differentiation is essential for deciding the right choice of treatment.
- In the absence of molecular genetic analysis in poor socioeconomic conditions, careful histopathological and immunohistochemical studies might be a key to establishing the diagnosis.

Features in previously published reports include large masses of heterogeneous architecture with areas of internal haemorrhage and necrosis, but no signs of extensive parenchymal or hilar infiltration.¹⁵

The primary treatment strategy is surgical resection with adjuvant chemotherapy. The role of radiotherapy is uncertain but nonetheless has been used to treat local tumour progression; however, no randomised clinical trials are available to validate this because of the rarity of renal ES/PNET. Adjuvant chemotherapy regimens have included vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide, but the combination of drugs used has varied broadly among different centres.¹⁶ Renal ES/PNET usually shows a poor prognosis with recurrence and metastases comprising more than 50% of clinical presentations. In a recent review of 26 cases, the mean patient survival was approximately 10 months.¹⁷ The fact that the tumour was incidentally discovered in our patient who had no regional or metastatic disease is noteworthy. Therefore, accurate diagnostic measures, such as imaging, biopsy and histopathology are crucial for timely management.¹²

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