CASE REPORT

Small Cell Variant of Anaplastic Large Cell Lymphoma with Positive Immunoreactivity for CD99

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SUMMARY

A 13 year old boy presented with a huge mass on his right arm of 6 months duration. Histopathological examination revealed sheets of malignant small round blue cells with immunopositivity for LCA, CD43, CD45Ro, CD30, EMA, ALK-1 and CD99, and negativity for CD20, TdT, myogenin, myoD1, NSE, bcl-6, bcl-2 and CD10. Fluorescent In-Situ Hybridization (FISH) testing excluded the diagnosis of Ewing's sarcoma/PNET. Pathologists need to be aware of the diagnosis of a small cell variant of ALCL, as well as of the fact that CD99 expression commonly occurs in cases of ALK-positive ALCL, in order to distinguish this entity from Ewing's sarcoma/PNET.

KEY WORDS:
Anaplastic large cell lymphoma, Small cell variant, CD99 positive, CD30 positive, Soft tissue tumour

INTRODUCTION

Anaplastic large cell lymphoma (ALCL) is a high-grade lymphoma characteristically showing a pleomorphic CD30 (Ki-1) positive large cell infiltrate, with a predominantly T-cell immunophenotype and co-expression of epithelial membrane antigen (EMA)[1]. Several variants of ALCL have been described, including monomorphic, Hodgkin's-related, lymphohistiocytic, sarcomatoid, and more recently, a biologically aggressive small cell variant (SCV)[2,3]. The SCV may progress to ALCL, but little is known about the transformation process and its significance[3]. We report a case of a small cell variant of ALCL, which presented as a huge mass on the right arm of a 13 year old boy, and which was immunoreactive for CD99.

CASE REPORT

A 13 year old boy presented with a huge 18 x 20cm mass on his right arm of six months duration. MRI showed an enhancing soft tissue tumour involving the whole triceps with no bony involvement. Histopathological examination of an open biopsy specimen revealed sheets of malignant small round blue cells with marked apoptosis, numerous mitoses and necrosis. Immunohistochemistry demonstrated positivity for LCA, CD43, CD45Ro, CD30 (Ki-1), EMA, ALK-1 and CD99 (figure 1), with negativity for CD20, TdT, myogenin, myoD1, NSE, bcl-6, bcl-2 and CD10. Fluorescent In-Situ Hybridization (FISH) testing showed a t(2;5)(p23;q35) translocation, which confirms a diagnosis of anaplastic large cell lymphoma, and excludes a diagnosis of Ewing's sarcoma/PNET (Figure 2). He was started on chemotherapy, the mass resolved, and his general condition markedly improved. Unfortunately, he later developed neutropenic sepsis after one of the chemotherapy regimes, and died from septic shock.

DISCUSSION

ALCL occurs in all age groups, with approximately 20% of cases being under 20 years. ALCL is recognized by a pleomorphic, large cell infiltrate; sinus or paracortical growth; and strong expression of CD30. Histologic variants include pleomorphic, monomorphic, HD-related, lymphohistiocytic, and sarcomatoid forms[1]. In 1993, Kinney *et al* reported a small cell variant (SCV) that was composed predominantly of small, irregular lymphocytes with a minor population of large CD30 positive cells[3]. Several studies have indicated that SCV is part of the histological spectrum of ALCL: the tumour cells are CD30 and EMA-positive, as in typical ALCL; while cytogenetic analysis shows characteristic t(2;5)(p23;q35) in some of the cases tested[4].

Clinically, the SCV is a biologically aggressive Ki-1 positive lymphoma with an overall 2-year survival of 50%, compared with 73% in prototypic or classic ALCL[2]. Some patients with SCV initially have widespread disease, including involvement of the lymph nodes, skin, liver, marrow and blood with rapid progression, but the lack histologic evidence of transformation[3]. Hodges *et al* demonstrated histologic transformation in 4 out of 17 (24%) of SCV cases, with a time to transformation of 1 to 146 months after diagnosis. After transformation, the course was very aggressive, and all but one patient died within a year. Comparison of histologic findings from the initial biopsy from the four patients with transformation to the 13 without transformation showed that necrosis, seen in 3 of 17 SCV, two of which later transformed, may be predictive of transformation. No other histologic or clinical features predictive of transformation were identified[1].

CD 99 (MIC2) is a 32-kDa transmembrane sialoglycoprotein that is expressed on many types of human cells, but shows strong expression in relatively few cell types, such as bone marrow progenitor cells, pancreatic islet cells, granulosa cells

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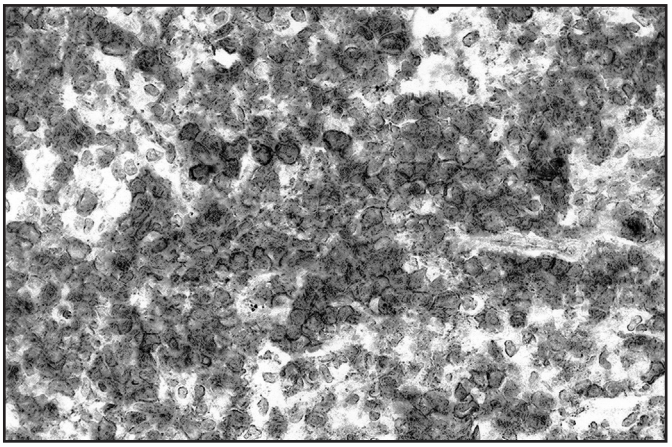

Fig. 1: The small round malignant cells show strong cell membrance positivity for CD99. (x200)

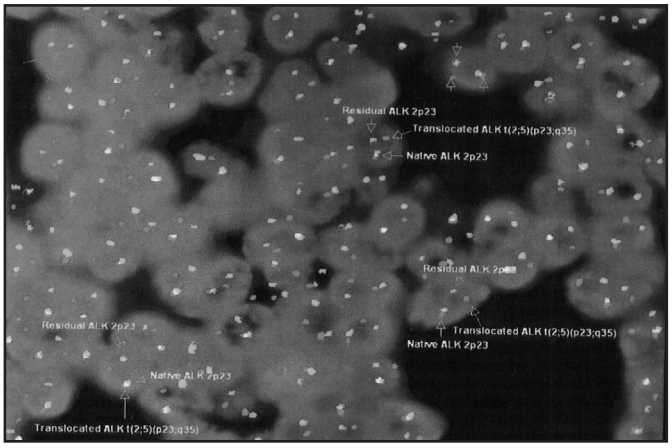

Fig. 2: Fluoresent In-Situ Hybridization test a t(2;5) (p23;q35) translocation.

of the ovary, and Leydig and Sertoli cells of the testis and ependyma[5]. CD99 (MIC2) was originally described as a diagnostically useful marker for Ewing's sarcoma/PNET and is currently used by most pathologists in this respect. However, it has also been documented in a variety of other tumours, notably hematologic neoplasms such as T and B lymphoblastic lymphomas/leukemias, acute myelogenous leukemia and chronic myelogenous leukemia in blastic crisis[5]. The expression of CD99 in non-Hodgkin lymphomas, other than the lymphoblastic type has become a subject of debate. A recent study by Sung *et al* revealed unexpectedly high expression of CD99 (70%) in ALK-positive ALCLs (compared to 20% in ALK-negative ALCLs), but negativity in other mature T/NK cell neoplasms[5]. The reason is unexplained, but the role of ALK is highly suggestive.

In this case, the patient presented with a huge 18x20cm mass on his right arm. MRI showed an enhancing soft tissue tumour involving the whole triceps with no bony involvement. The initial clinical impression was that of a rhabdomyosarcoma. Histopathological examination revealed sheets of malignant small round blue cells with marked apoptosis, numerous mitoses and necrosis. Immunohistochemistry demonstrated positivity for LCA, T cell markers, CD30 (Ki-1), EMA, ALK-1 and CD99 (Figure 1), with negativity for B cell, myogenic and neuroendocrine markers, as well as the other small cell lymphomas. Fluorescent In-Situ Hybridization (FISH) testing showed a t(2;5)(p23;q35) translocation, which confirmed a diagnosis of anaplastic large cell lymphoma, and excluded a diagnosis of Ewing's sarcoma/PNET (Figure 2).

Pathologists need to be aware of the entity of small cell variant of anaplastic large cell lymphoma when considering the differential diagnosis of small round blue cell tumours, as the appearance of small cells seen on routine hematoxylin & eosin (H&E) would not normally bring to mind a differential diagnosis of anaplastic large cell lymphoma. However, the presence of immunopositivity for both LCA and CD99 in the initial immunohistochemical work-up of a small round blue cell tumour should raise a suspicion of this diagnosis, to be then confirmed with immunomarkers for CD30 (Ki-1) and ALK. FISH testing is also invaluable in confirming the diagnosis, and to definitively exclude a diagnosis of Ewing's sarcoma/PNET.

CONCLUSION

Pathologists need to be aware of the diagnosis of a small cell variant of ALCL, as well as of the fact that CD99 expression commonly occurs in cases of ALK-positive ALCL, in order to distinguish this entity from Ewing's sarcoma/PNET.

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