CASE REPORT

Terminal deoxynucleotidyl transferase (TdT)-negative T-cell lymphoblastic lymphoma with loss of the T-cell lineage-specific marker CD3 at relapse: a rare entity with an aggressive outcome

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SUMMARY

Terminal deoxynucleotidyl transferase (TdT)-negative T-cell lymphoblastic lymphoma is a variant of T-cell lymphoblastic lymphoma/T-cell lymphoblastic leukaemia. TdT is a marker of immaturity expressed in 90%–95% cases of lymphoblastic lymphoma and useful in differentiating it from other mature lymphomas/leukaemias. It has been associated with poorer response to chemotherapy and a more aggressive outcome. Here we present a case of TdT-negative T-cell lymphoblastic lymphoma in a 28-year-old man who presented with superior vena cava syndrome. The patient was treated with hyper-cyclophosphamide, vincristine, Adriamycin, dexamethasone (CVAD), however unfortunately suffered a relapse 1 year later. A unique feature of our case was that on relapse, the patient lost expression of the T-cell lineage-specific marker CD3, which has previously not been reported in association with TdT-negative T-cell lymphoblastic lymphoma. The patient failed to respond to chemotherapy on his relapse and died.

BACKGROUND

T lymphoblastic leukaemia (T-ALL)/T lymphoblastic lymphoma (T-LBL) is an aggressive neoplasm of immature T cells involving bone marrow and blood (leukaemia) or presenting as an anterior mediastinal mass or involvement of nodal and extranodal sites (lymphoma).¹ T-ALL is more common in adolescent males and constitutes approximately 25% cases of adult acute lymphoblastic leukaemia (ALL).² T-LBL with 26% of 5-year overall survival rate constitutes approximately 85%–90% of all lymphoblastic lymphomas and is also more common in adolescent males, similar to its leukaemic counterpart.^{1 2} Morphologically, lymphoblasts are small to intermediate sized, having irregular convoluted nuclei, indistinct nucleoli and scant cytoplasm.¹ Mitotic activity is brisk and tangible body macrophages, when present, impart starry sky appearance similar to Burkitt lymphoma.¹ Morphologically, T-LBL is indistinguishable from T-ALL and B-cell lymphoblastic lymphoma.¹ Terminal deoxynucleotidyl transferase (TdT) is a marker of immaturity

expressed in 90%–95% cases of lymphoblastic lymphoma and useful in differentiating it from other mature lymphomas.^{3 4} TdT-negative T-ALL/LBL, however, is a rare entity with occasional case reports and series in the literature.⁵ It progresses at a higher rate and is associated with shorter overall survival.⁵ We report TdT-negative T-LBL in a 29-year-old man with an aggressive outcome that was associated with loss of CD3 expression on relapse.

CASE PRESENTATION

A 28-year-old man presented to the emergency unit with 1-month history of progressive facial swelling, dyspnoea, chest pain, cough and light headedness. Physical examination revealed distension of neck veins, facial oedema, plethora and papilloedema with aggravation of symptoms on lying down (figure 1). Chest X-ray showed bilateral pleural effusion. CT scan of the chest revealed a large 9.6×8.3×7.8 cm soft tissue density mass in mediastinum causing superior vena cava encasement and compression with multiple engorged collateral vessels in right anterior, lateral and posterior chest wall with soft tissue oedema. Bilateral multiple prominent subcentimetre axillary lymph nodes were also noted. Superioanteriorly a mass was extending up to retrosternal level with loss of fat planes with superioanterior pericardial margins. Inferiorly it was extending up to carinal and short segment of subcarinal level and was causing mild compression of trachea and carina. Bilateral pleural effusions were noted. Right internal jugular vein dilatation and multiple bilateral enlarged subcentimetre cervical lymph nodes were also seen. Abdominal imaging was unremarkable. Differential diagnosis at this time were of a lymphoma or a thymic neoplastic mass.

INVESTIGATIONS

Incisional biopsy of mediastinal mass revealed a malignant tumour infiltrating fibrocollagenous tissue with extensive crushing artefacts (figure 2). It consisted of dyshesive round to oval cells with hyperchromatic nuclei, coarse chromatin and high N/C (nucleus/cytoplasm) ratio. Mitotic figures were also noted (figure 3). On

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Figure 1 Superior vena cava syndrome.

immunohistochemistry, the tumour cells were strongly positive for CD45, CD3 and CD34 (figures 4 and 5). TdT was repeated twice and was negative (figure 6). CKAE1/AE3, CD20, CD99, CD68, CD117, CD56 and myeloperoxidase (MPO) were also negative. MIB-1 was 85%–90%. Based on morphology and immunohistochemistry, the tumour was diagnosed as TdT-negative T-cell lymphoblastic lymphoma. Bone marrow aspiration and trephine biopsy revealed a normocellular bone marrow with no evidence of lymphoproliferative disorder. The patient dramatically responded to hyper-CVAD chemotherapy. After 1 year, he presented with subcutaneous soft tissue nodules in right breast and anterior chest wall (figure 7) along with multiple enlarged left axillary (largest 1.4 cm) and anterior mediastinal lymph nodes (largest 3 cm). Trucut biopsy of the chest wall mass reveal similar morphology. Now this time on immunohistochemistry, along with the negativity of TdT, CD99, CD20, CD79a, PAX5, CD68, CD117, CD30 and MPO, CD3 was also found to be negative. The only positive marker was CD34. Bone marrow aspiration and trephine biopsy was again negative.

DIFFERENTIAL DIAGNOSIS

Before biopsy, our differential diagnosis was lymphoma and thymoma based on CT scan. After biopsy, lymphoma was

Figure 2 H&E section at ×4 magnification showing crushing artefact.

Figure 3 H&E section at ×40 magnification showing small cells with rounded nuclei and scant cytoplasm.

on top of our differentials followed by thymoma, myeloid sarcoma and blastic plasmacytoid dendritic cell neoplasm. Thymoma was excluded by negativity of CKAE1/AE3 and TdT. Myeloid sarcoma was excluded by positivity CD3 and negativity of MPO and CD68, whereas blastic plasmacytoid dendritic cell neoplasm was excluded by negativity of CD56.

TREATMENT

The patient was again treated with hyper-CVAD on relapse however failed to respond to chemotherapy.

OUTCOME AND FOLLOW-UP

Recurrence occurred in our patient after 1 year and who then died after 8 months without responding to repeat chemotherapy.

DISCUSSION

Although the morphology of cells was mostly obscured by crushing artefacts, based on clinical presentation with anterior mediastinum mass along positivity of tumour cells for CD45,

Figure 4 CD3 immunohistochemistry stain showing strong and diffuse positivity.

Figure 5 CD34 immunohistochemistry stain showing strong and diffuse positivity.

CD3, CD34 and negativity for TdT, we diagnosed our case as TdT-negative T-LBL.

Immunohistochemistry has an important role in the diagnostic work-up of T-ALL/LBL. It shows variable expression of CD2, CD3, CD4, CD5, CD7 and CD8.² Only CD3 is considered to be lineage-specific marker of T cells with cytoplasmic and/or membranous positivity.² T-ALL/LBL express one or more markers of immaturity including TdT, CD99, CD34, CD1a, with CD99 being the most important after TdT.^{2,5} Aberrant expression of myeloid antigens (CD33, CD13, etc) and B-cell markers (CD79a) can be seen; however, this aberrant expression is less likely in TdT-negative LBL.³ Our case was initially positive for CD3 but at relapse, its expression was lost. Second, CD34 was positive both at initial presentation and at relapse. CD99 and CD1a were negative. B-cell lymphoma was excluded by the negativity of CD20 and CD79a. Myeloid sarcoma was excluded by the negativity of CD68, MPO and CD117, and positivity of CD3, although aberrant expression of T-cell markers can be seen.⁶ Blastic plasmacytoid dendritic cell neoplasm (blastic NK cell lymphoma) was excluded by the negativity of CD56 and positivity of CD3.⁷ Terada *et al* described a case of TdT-negative T-LBL that expressed Platelet Derived Growth Factor Receptor

Figure 6 Negativity of terminal deoxynucleotidyl transferase immunohistochemistry stain.

Figure 7 Recurrence after 1 year.

Alpha (PDGFRA) also. Because the gene of PDGFRA is located close to cellular KIT (c-KIT), the expression of the latter resulted in PDGFRA expression.⁸

TdT is a specialised DNA polymerase involved in the addition of nucleotides at 3' terminus of a DNA primer during genetic recombination, which in contrast to DNA polymerase do not require template information for polymerisation.⁹ It is a nuclear protein expressed in immature thymocytes, transformed pre-B and pre-T lymphoid cells, ALL/lymphoma cells and in a minor fraction of bone marrow lymphocytes.⁹ It is expressed in 90%–95% cases of lymphoblastic lymphoma^{3,4}; however, a negative expression cannot rule out the diagnosis of T-ALL/LBL.^{2,4,10} Therefore, other markers of immaturity (CD99, CD34, etc) should be performed in suspected cases of a T-LBL negative for TdT.

Apart from TdT negativity, another peculiar feature of our case was that our patient was aleukaemic at presentation and even after a relapse. Bone marrow aspiration and trephine biopsy were normocellular with no evidence of blasts. A similar case of TdT-negative T-LBL in an adolescent who presented with supraclavicular lymphadenopathy without bone marrow and peripheral blood involvement is also described which along with CD3 and CD34 positivity also expressed CD99 as well.¹¹

Another unique feature of our case was a loss of T-cell lineage-specific marker (CD3) after multidrug chemotherapy. Immunophenotypic differences or antigenic shifts are reported in ALL after induction chemotherapy. In a prospective study of 54 children with lymphoid malignancies, Borella *et al* described antigenic shifts in three patients.¹² In the first case, T-antigen positivity occurred in lymphoblasts at relapse who initially had null cell ALL at diagnosis. In the second case, loss of IgD occurred at relapse in a B cell lymphoma who initially expressed both IgM and IgD. While in the third case, there was a loss of expression of E receptor at relapse in T-ALL. Tomová and Babusíková found antigenic shifts in 42 out of 58 patients of both ALL and acute myeloid leukaemia (AML).¹³ Analysis of 3 of the 20 cases of T-ALL at relapse revealed loss of CD1 and CD2 in two cases while in the third case loss of CD10, CD13 and CD34

was observed along with the gain of expression of non-lineage specific markers, that is, CD71 and CD38.¹³ Thus, problems may occur in predicting relapse in such patients with antigenic shifts.¹³ In patients of T-ALL who were enrolled in Children's Oncology Group Protocol (COG-AALL0434) for treatment of T-ALL, markers associated with immaturity (TdT, CD99) were lost in leukaemic blasts while expression of lineage-specific markers (CD2, CD3, CD4, CD5, CD7, CD8) was found to be stable during induction chemotherapy.¹⁴

Non-Hodgkin's lymphoma (NHL) type regimens, ALL type regimens and pediatric-inspired ALL regimens with/without prophylactic cranial irradiation and with/without prophylactic or therapeutic mediastinal irradiation are the therapeutic approaches used in the treatment of LBL, but standard treatment protocols remain to be established for adult patients with T-LBL.^{15,16} Lower rates of complete remission and disease-free survival were observed in NHL type regimen.¹⁶ Using ALL-type regimen improvements were noted in long-term outcomes both in children and adults.¹⁶ After the success of paediatric-inspired ALL regimens in ALL, GRAALL-LYSA LL03 study first evaluated its efficacy in 148 untreated patients of LBL (131 T-LBL, 17 B-LBL) and found good response rate and outcome.¹⁷ The 3-year event-free survival, disease-free survival and overall survival were 63.3%, 72.4% and 69.2%, respectively, in these patients.¹⁷ Central nervous system (CNS) prophylaxis with high-dose systemic chemotherapy and intrathecal chemotherapy is also suggested as the CNS relapse rate range from 42% to 100% when no prophylaxis is done.¹⁶ Mediastinal radiotherapy is not routinely suggested in LBL and rather should be reserved for selected patients.¹⁶ Residual mediastinal tumours are managed either by local radiotherapy or by its surgical resection.¹⁶ The patient should be closely observed if he/she is on maintenance chemotherapy or is undergoing stem cell transplantation.¹⁶ Long-term prognosis may be improved with intensive consolidation therapy followed by autologous or allogeneic stem cell transplantation but it remains a matter of debate that which patients benefit from SCT.¹⁶ No standard therapeutic options for relapsed LBL cases have been defined so far.

We described a rare case of TdT-negative T-cell LBL who initially showed a dramatic response to hyper-CVAD chemotherapy but the disease recurred after 1 year. He did not respond to hyper-CVAD chemotherapy and died after 8 months. He was

aleukaemic both on initial presentation and recurrence. Moreover, our case showed a unique antigenic shift (loss of CD3 at relapse) which, to the best of our knowledge, is not reported yet.

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Learning points

- Terminal deoxynucleotidyl transferase (TdT)-negative lymphoblastic lymphoma (LBL) is a rare entity with aggressive clinical outcome.
- The diagnosis of LBL cannot be excluded just by the absence of TdT expression. Other markers of immaturity like CD34, CD99 and CD1a should be applied.
- Loss of T-cell marker CD3 can rarely occur after chemotherapy.

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