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Case Report

Cyclin D1 expression in Peripheral T-Cell Lymphoma: A report of 2 cases

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ABSTRACT

Background: Peripheral T-cell lymphomas (PTCLs) represent a heterogeneous group of non-Hodgkin's lymphomas (NHL), characterized by poor outcome, accounting approximately for 10%-15% of all non-Hodgkin lymphomas in the western countries, and with a higher prevalence in Asia. Cyclin D1 immunoreactivity is characteristically seen in mantle cell lymphoma. It is also observed in hairy cell leukemia, plasma cell myeloma and a proportion of diffuse large B-cell lymphomas, however its expression in peripheral T-cell lymphoma is rarely recorded.

Case Report: We report two cases of peripheral T-cell lymphoma not otherwise specified with heterogeneous nuclear Cyclin D1 immunohistochemical overexpression, due to gene copy gain, a phenomenon similar to that observed in Mantle Cell Lymphoma.

Conclusion: Cyclin D1 expression can be seen in PTCLs, besides mantle cell lymphoma, hairy cell leukemia and plasma cell myeloma and underline the importance of molecular biology integration tests as a diagnostic tool to escape the pitfall.

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1. Introduction

The cyclin proteins are important in the regulation of the cell cycle by activating cyclin dependent kinases at specific stages of the cell cycle, and thus promoting DNA replication and cell division. Mitogenic stimuli activate the tyrosine kinase receptor which triggers a signaling cascade, resulting in upregulation of cyclin D1. Aberrant expression of cyclin D1 can be due to chromosomal translocations, gene amplification or copy gains.¹ The deregulation of cyclin-dependent kinases can lead to cancer by causing proliferation that is independent of the checkpoints and regulators. Genomic alterations such as the t(11;14)(q13;q32), which juxtaposes the cyclin D1-encoding gene (CCND1) to the immunoglobulin heavy chain gene are characteristic for mantle cell lymphoma.²

Although cyclin D1 protein expression is well characterized in solid tumors and B-cell lymphomas, there is little data regarding cyclin D1 expression in peripheral T-cell lymphomas.^{3,4} The identification of cyclin D1 has treatment implications because cyclin D1 can be a therapeutic target.

2. Case History

In this case report, we describe 2 cases of peripheral T cell lymphoma with remarkable expression of cyclin D1.

2.1. Case 1

A 54-year-old man was admitted because of multiple superficial adenopathies, splenomegaly and bilateral lower limbs lymphedema. Laboratory data revealed elevated LDH levels. Peripheral blood counts were normal. Parameters are as follows: white blood cells count (WBC) 8500/mmc (neutrophils 73.5%; Leukocytes 20.8% Monocytes 5,5%);

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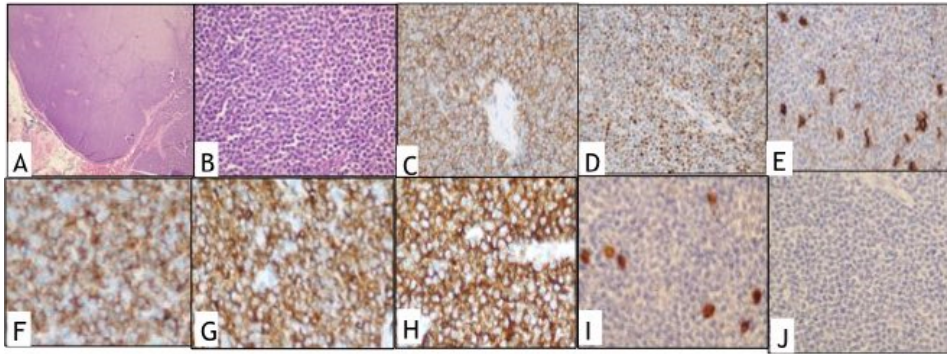


Fig. 1: Photomicrographs of Peripheral T-cell lymphoma morphology and immunostaining - Case1: **A** and **B**: hematoxylin and eosin morphology 5X and 40X magnification respectively; **C**: CD5 positivity (20X magnification); **D**: Cyclin D1 immunostaining positivity (20X magnification); **E**: CD20 immunostaining negativity (40X magnification); **F,G,H,I**: CD3,CD2,CD4,CD8 immunostaining positivity (40X magnification); **J**: SOX11 immunostaining negativity (40X magnification).

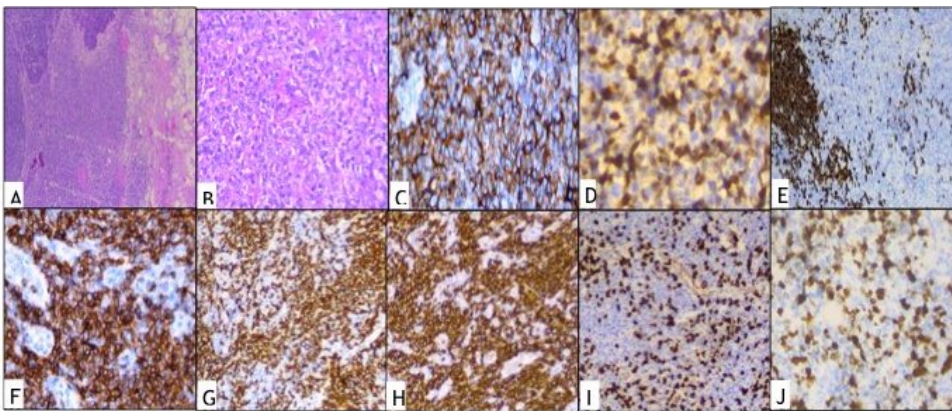


Fig. 2: Photomicrographs of Peripheral T-cell lymphoma morphology and immunostaining – Case 2: **A** and **B**: Hematoxylin and eosin morphology 5X and 40X magnification respectively; **C**: CD5 positivity (20X magnification); **D**: Cyclin D1 immunostaining positivity (20X magnification); **E**: CD20 immunostaining negativity (40X magnification); **F,G,H,I**: CD3,CD2,CD4,CD8 immunostaining positivity (40X magnification); **J**: Mib1 expression (40X magnification).

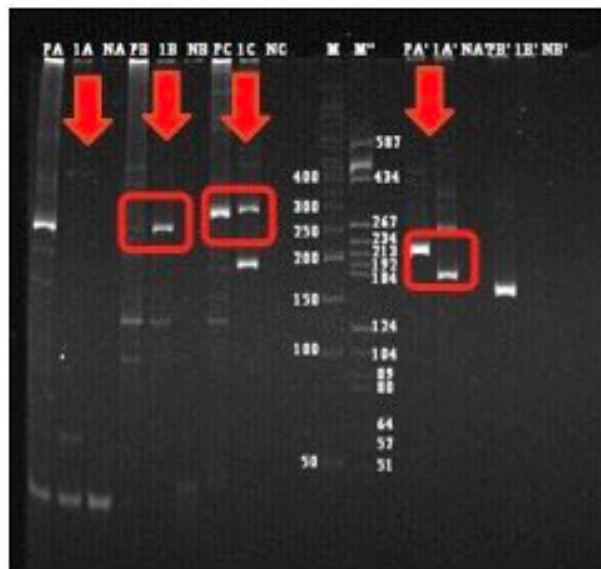


Fig. 3: Molecular analysis exhibiting rearranged T-cell receptors (both beta and gamma)

red blood cells count (RBC) 3.97/mmc Haemoglobin (Hb) 13.4 g/dl; Platelet count (PLT) 129.000/mmc. CT (computed tomography) scan showed multiple deep and superficial lymph-nodes enlargement of inguinal, axillary and abdominal region. An inguinal nodal biopsy was performed for diagnosis purpose.

2.2. Case 2

A 52-year-old with gradually increasing left cervical lymphadenopathy presented in outpatient department. On work-up, LDH levels were elevated with hyperuricemia. Peripheral blood counts were within normal limits (Total leucocyte count: 11,100/cmm, Hb:12.4g/dl, Platelet count (PLT):156.000/mmc). Left cervical lymph node was subjected for histological examination.

On the basis of this clinical presentation and histological findings was excluded a diagnosis of lymphoma with a leukemic presentation. On histological examination, both the lymph node biopsies showed a diffuse infiltrate of medium sized lymphoid cells with folded nuclear membranes, vesicular nuclear chromatin, inconspicuous nucleoli and a thin rim of eosinophilic cytoplasm; morphologically resembling mantle cell lymphoma. The tumor cells co-expressed CD5 and cyclin D1, however, surprisingly they did not express CD20. The cells were also negative for Pax5. Instead, they expressed T-cell associated markers- CD3, CD2 and CD7. CD4/CD8 analysis revealed CD4 predominant pattern of expression. The lymphoid cells did not express CD79a, CD10, TdT or CD34. Importantly, the lesional lymphoid cells did not express SOX11. The proliferation marker MIB1 was positive in almost 30% of cells in the second case. Therefore, these cases were diagnosed as non-Hodgkin lymphoma of peripheral T-cell type, NOS with cyclin D1 expression. (Figures 1 and 2)

TCR gene receptor rearrangement studies revealed rearrangement of both beta and gamma T-cell receptors (Figure 3) in one tested case (case 1).

The patient with inguinal lymph node enlargement was placed on GEMOX chemotherapy regimen (gemcitabine and oxalyplatin). Only one cycle of therapy was administered because of haematological and systemic toxicity, the patient died of disease two months after the diagnosis. While the patient with cervical lymphadenopathy, underwent chemotherapy: responded well and is doing well till date.

3. Discussion

Cyclin D1 protein expression is commonly seen in B-cell neoplasms, classically in mantle cell lymphoma but also in hairy cell leukemia and plasma cell myeloma⁵. It is seen in various normal tissues like salivary duct cells, gastric epithelium, tubular epithelium in kidney, epithelial cells of terminal bronchiole⁶ as well as in non-hematological malignancies (non-small cell lung cancer, breast cancer, esophageal cancer, melanoma).⁷ In this case report, we

highlight that expression of cyclin D1 is not limited to B-cell lymphomas, but can also be seen in peripheral T-cell lymphomas.

Peripheral T-cell lymphomas (PTCLs) represent a heterogeneous group of non-Hodgkin lymphomas (NHL), characterized by poor outcome, accounting approximately for 10-15% of all non-Hodgkin lymphomas in the western countries, and with higher prevalence in Asia.^{8,9} These are highly aggressive and show poor response to therapy and frequent relapses.¹⁰ Cyclin D1 G/A870 polymorphism has been implicated as a modulator of cancer risk and/or poor prognosis in human disease.¹¹ Cyclin D1 overexpression is not specific to any particular cancer, it is important in oncogenesis and proliferation of many tumors. Therefore, Cyclin D1 overexpression is a potential therapeutic target using agents that target the cyclin-dependent kinase pathway.¹² Staining for cyclin D1 protein in peripheral T-cell lymphomas may identify patients who might benefit from therapies that target cyclin D1 or its associated cyclin-dependent kinases.¹³

4. Conclusion

In this case report, we emphasize the fact that the diagnostic pitfall represented by Cyclin D1 immunohistochemical overexpression in a T-cell lymphoma. Several pitfalls could lead to misinterpretation of diagnosis; therefore, we underlined the need to integrate the classical histology and immunohistochemistry with molecular tests as clonality or Fluorescence in situ hybridization.

5. Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

6. Source of Funding

None.

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