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Case Report

Mixed phenotypic (T cell/B cell) lymphoblastic lymphoma of synovium, report of the first case with discussion on potential diagnostic pitfalls

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ABSTRACT

Mixed- phenotype acute leukaemia (MPAL) is very rare and accounts for less than 4% of acute leukaemia. Most cases of MPAL described in literature, are of T/myeloid or B/myeloid phenotype. MPAL T/B cell lineage is exceptional and occasional cases reported so far, are leukaemia with bone marrow involvement. Our case, on immunophenotyping, exhibited evidence of T and B- Lymphoid lineage. It could be diagnosed neither as MPAL, because the bone marrow was not involved, nor as lymphoblastic lymphoma because of the bi phenotypic expression of both T and B cell antigens. Hence, we reported it as Mixed phenotypic (T cell/B cell) Lymphoblastic Lymphoma. This is the first case, extra medullary as well as extra lymphoid in location, presenting as right elbow synovial lesion. We also discuss the potential diagnostic pitfalls and emphasise the importance of Immunohistochemistry in diagnosis of lymphoblastic lymphomas.

1. Introduction

Mixed- phenotype acute leukaemia (MPAL) T/B cell lineage is extremely rare and the characteristics like Epidemiology, clinical presentation, prognosis of such cases are not reported in literature.[1] MPAL refers to leukaemia that contain blasts, which express antigens of more than one of the three lineages namely; Myeloid, T cell and B cell.[2] MPALs can have distinct population of blasts, each group of a different lineage (previously called as acute bilineal leukaemia) or a single population of blasts with the same cell expressing multiple antigens of diverse lineages (previously called as biphenotypic leukaemia), or a combination of both.[3] Ambiguity of antigen expression commonly involves the myeloid lineage coexisting with either B-cell or T-cell lineage, nevertheless exceptional cases of ambiguity between B and T cell antigens too occur.[4] In certain sites and scenarios, Immunohistochemistry with markers like Cluster of differentiation (CD) CD99 and Friend Leukaemia Integration-1 (FLI-1) has potential pitfalls and hence the panel of antibodies should be carefully chosen, to arrive at a diagnosis.[5] Immunophenotyping plays a very vital role in assignment of such cases to mixed phenotypic category. Their recognition is crucial, because such patients have poor prognosis, require intensive chemotherapy, many are resistant to treatment and generally have a poor outcome.[6]

2. Case Presentation

A 15-year-old boy presented with complaints of swelling in the right elbow joint of 3 months duration. Magnetic Resonance Imaging (MRI) scan revealed mild humeroulnar joint effusion with synovial thickening, mild altered signals in lower one third of Humerus with periosteal reaction, suggestive of an infective aetiology and hence a synovial biopsy was performed. Morphology on Haematoxylin & Eosin stained slide (Figure 1 a and 1b) revealed a neoplasm composed of diffuse sheets of small round cells with focal crush artefact, favouring a differential diagnosis of Ewing's sarcoma and lymphoblastic lymphoma. Hence

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we proceeded with Immunohistochemistry for a definitive diagnosis, which was performed on automated Roche Ventana Benchmark GX. The preliminary panel of markers chosen were CD 99 (O13 clone), LCA (2B11+PD7/26 clone) and Vimentin (EP21 clone). This revealed a CD 99 positive (Figure 2 a), Vimentin positive (Figure 2 b) and LCA negative tumour, favouring a diagnosis of Ewing's sarcoma. Next an panel of immunohistochemical markers comprising of FLI-1 (G146-22 clone), TdT (EP266 clone), CD34 (QBEnd/10 clone), CD3 (Polyclonal), CD 20 (L26 clone) and then subsequently CD 19(LE-CD19 clone) and CD79a (SP18 clone) were performed. The results were as follows: FLI-1 positive, CD34 positive, TdT positive (Figure 3 a), CD3 positive (Figure 3b), CD19 positive (Figure 3c), CD79a positive (Figure 3d) and CD 20 was negative. The neoplasm was revealed to be an Acute lymphoblastic lymphoma/leukaemia, expressing both T and B cell antigens. Therefore, a bone marrow examination was requested for further evaluation. The bone marrow aspiration and bone marrow trephine biopsy (Figure 4a and 4b) performed, revealed a normocellular marrow with normal trilineage haematopoiesis, ruling out the possibility of leukaemia, hence could not be called MPAL and furthermore, because of co expression of both the T and B lymphoid lineage antigens, a final diagnosis of Mixed phenotypic Lymphoblastic lymphoma (T cell / B cell) was rendered. Two weeks post biopsy, repeat MRI scan revealed moth eaten destruction and cortical erosion involving the right distal humerus, proximal radius and ulna with surrounding soft tissue swelling, suggesting spread of tumour from synovium into both side bones. The patient was started on and is undergoing intense chemotherapy.

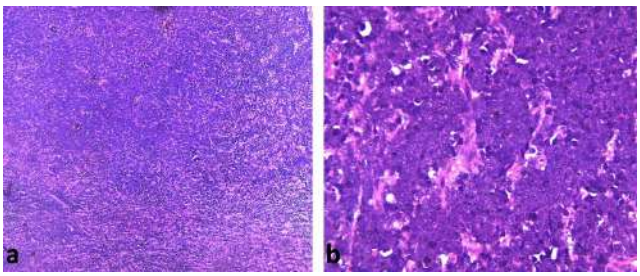

Fig. 1: Histology of synovial biopsy: a) Diffuse sheets of small round cells (H&E 10X) (b) Cells showing scant amounts of eosinophilic cytoplasm, round nuclei with conspicuous nucleoli in some (H&E 40X).

3. Discussion

The 4^{th} edition of World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues proposed new consensus criteria to diagnose MPAL[1] and in the updated 2016 classification, these criteria has been retained without modification.[6] According to

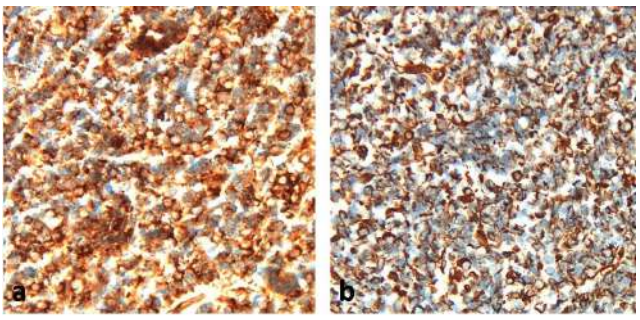

Fig. 2: Immunohistochemistry: **a)** Diffuse membranous staining for CD99 in tumour cells (IHC 40X); **b)** Tumour cells exhibiting diffuse positive staining for vimentin (IHC 40X)

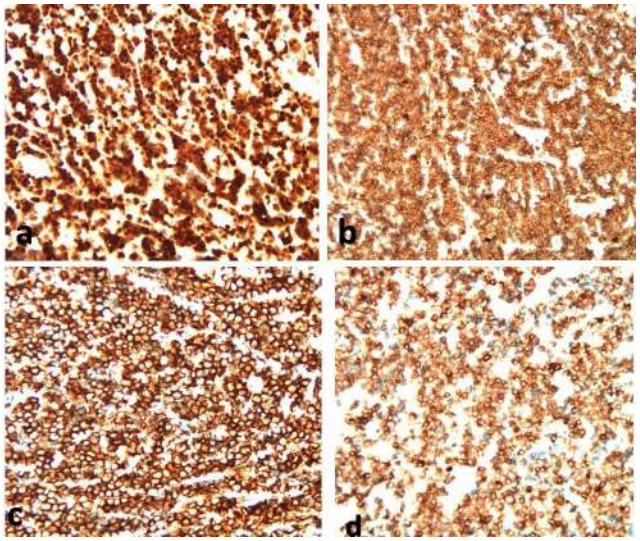

Fig. 3: Immunohistochemistry: **a):** Diffuse strong nuclear staining of tumour cells for TdT (IHC 40X); **b):** Diffuse strong membranous and cytoplasmic staining for CD3 in tumour cells (IHC 40X); **c):** Tumour cells exhibiting diffuse positive membranous staining for CD19 (IHC 40X); **d):** Diffuse strong membranous staining for CD79a in tumour cells.

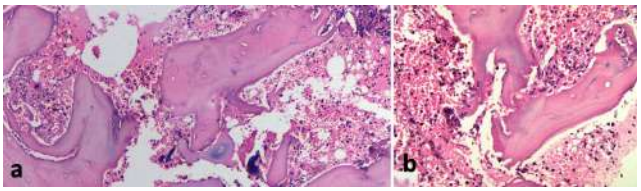

Fig. 4: Histology of Bone marrow trephine biopsy: **a)** Bony trabeculae enclosing normocellular marrow spaces (H&E 10X); **b)** Trilineage hematopoiesis with erythroid, megakaryocyte and myeloid series of cells (H&E 40X).

WHO, Myeloperoxidase is the most specific marker for myeloid lineage. Although expression of any two of the markers: CD11c, CD14, CD64, NSE and lysozyme is also used to assign myeloid lineage. Diagnosis of T cell lineage requires cytoplasmic or surface expression of CD3 antigen while confirmation of B cell lineage mandates strong CD19 expression along with presence of any one of the three antigens CD79a, CD22 or CD10.[6] Our case had expression of TdT and CD34, which established the diagnosis of Lymphoblastic Lymphoma along with the expression of T cell antigen CD3 and B cell antigens CD19 and CD 79a, substantiating our diagnosis of Mixed phenotypic Lymphoblastic lymphoma, T/ B cell phenotype.

WHO Classification of hematopoietic and lymphoid tumours, 2016, classifies MPAL into five types namely: MPAL with t (9; 22) (q34; q11.2), MPAL with MLL rearrangement, MPAL B/myeloid not otherwise specified (NOS), MPAL T/myeloid NOS, and MPAL NOS rare types.[6] The common types are MPAL B/myeloid NOS, accounting for 1% of cases, more common in adults, have clonal cytogenetic abnormalities, complex karyotype, has poor outcome[7] and MPAL T/myeloid, NOS accounting for less than 1% of all cases, slightly more common in children, similarly has a poor prognosis.[8] MPAL NOS other rare types, like T / B cell is very rare and only 29 cases are reported in literature so far; Single case reports include those by, Costa et al.[9] in 2008, Naghashpour et al.[10] in 2010, Kohla et al[11] and Sharma et al[12] in 2015, Pawar et al[13] in 2017. Larger cohorts include 3 cases reported by Gujaral et al[14] in 2009, 4 cases contributed by Matutes et al[15] in 2011, 9 cases by Mi et al[16] and 8 cases by Alexander et al[17] in 2018. All these cases have intra medullary involvement, presenting as acute leukaemia. Our extensive literature search did not reveal any case of extra medullary and extra lymphoid MPAL T/B cell type reported in literature, so far.

In a study of MPAL in paediatric cases, Rubnitz et al identified that T cell / myeloid is the most common phenotype in children.[18] Our case was a 13-year-old boy, presenting with T cell / B cell phenotype.

Even though the presumed cell of origin of MPAL is unidentified, it is probable that this arises in an early haematopoietic, common lymphoid progenitor cell that has the potential to undergo either B cell or T cell differentiation.[19]

Extra medullary location of MPAL is even rarer, with most common location being lymph node. Vega et al reported six cases of t (8:13) positive, T/myeloid MPAL, out of which five occurred in lymph node and one in breast.[20] To the best of our knowledge, case of extra medullary, extra lymphoid MPAL NOS, other rare types is not reported, so far. Our case is extra medullary as well as extra lymphoid MPAL T/B cell type, of the synovium of right elbow joint.

CD45 negative, CD99 positive and FLI-1 positive, Lymphoblastic lymphoma (LL) cases has been reported in literature. This is a potential diagnostic pitfall, leading to misdiagnosis of Ewing sarcoma (ES).[21] Lin et al in their study, observed high FLI-1 positivity in Acute Lymphoblastic lymphoma / leukaemia and T cell lymphoma cases. Hence, they concluded that LCA negativity cannot rule out lymphoblastic lymphoma and FLI-1 which was, once considered a specific marker of ES, should be used cautiously in differentiating ES from LL.[22]

Differentiating cases of (LL) from (ES) is tricky as they have overlapping morphology and Immunohistochemistry findings. However, this is crucial because of their different clinical behaviour and treatment. Lucas et al., studied 27 cases of LL, 17 cases of ES and observed that two cases of LL were initially misdiagnosed as ES. They concluded that a panel consisting of CD99, Terminal deoxy Transferase (TdT) and vimentin along with other lymphocytic markers is helpful in differentiating these two entities.[23] However, Terada reported a case of TdT negative, CD99 positive and CD34 positive, T Lymphoblastic lymphoma and suggested inclusion of other precursor cell markers like CD34, KIT in the LL diagnostic panel.[24]

In our case, Immunohistochemistry panel revealed a CD 99 positive, FLI-1 positive and LCA negative tumour, favouring the diagnosis of (ES), especially the site of biopsy, being synovium. However an adequate panel of markers used, helped in arriving at the correct diagnosis of lymphoblastic lymphoma.

Since both CD3 and CD79a were positive, a possibility of biphenotypic lymphoma was considered. However, transient and weak expression of CD79a is present in immature cells of T- cell lineage and hence cases of T cell Acute lymphoblastic leukemia /lymphoma, can show aberrant expression of CD79a.[25] Hence CD19 was performed, which was also positive, thus confirming the bilineage expression.

Cases of MPAL have a poor prognosis, are resistant to conventional chemotherapy, have an aggressive course and may require intensive therapy.[26] The initial MRI scan showed involvement of synovium, but the post biopsy MRI after two weeks showed spread to bones, thus suggesting an aggressive course.

4. Conclusion

Cases of Lymphoblastic lymphoma should be reported with an expanded panel of markers to avoid misdiagnosis. Reporting all such, cases of MPAL, encountered in routine practice, will aid to enrich the literature and subsequently help to unveil the clinical features and prognosis of these rare tumours in future.

5. Source of Funding

None.

6. Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. Borowitz MJ, Bene MC, Harris NL, Porwit A, Matutes E, Swerdlow SH, et al. Acute leukemias of ambiguous lineage. In: WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2008. p. 150–5.
2. Kim HJ. Mixed-phenotype acute leukemia (MPAL) and beyond. *Blood Res*. 2016;51(4):215–6. doi:10.5045/br.2016.51.4.215.
3. Nathan J, Charles, Daniel F. Boyer Mixed-Phenotype Acute Leukemia: Diagnostic Criteria and Pitfalls. *Arch Pathol Lab Med*. 2017;141(11):1462–8.
4. Weinberg OK, Arber DA. Mixed-phenotype acute leukemia: historical overview and a new definition. *Leuk*. 2010;24(11):1844–51. doi:10.1038/leu.2010.202.
5. Zhang PJ, Barcos M, Stewart CC, Block AW, Sait S, Brooks JJ. Immunoreactivity of MIC2 (CD99) in Acute Myelogenous Leukemia and Related Diseases. *Modern Pathol*. 2000;13(4):452–8. doi:10.1038/modpathol.3880077.
6. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Beau ML, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391–2405. doi:10.1182/blood-2016-03-643544.
7. Weir EG, Ansari-Lari MA, Batista DS, Griffin CA, Fuller S, Smith BD, et al. Acute bilineal leukemia: a rare disease with poor outcome. *Leukemia*. 2007;21(11):2264–70. doi:10.1038/sj.leu.2404848.
8. Lopes GS, de Vasconcelos Leitão J, Kaufman J, Duarte FB, Matos DM. T-cell/myeloid mixed-phenotype acute leukemia with monocytic differentiation and isolated 17p deletion. *Rev Bras Hematol Hemoter*. 2014;36:293–6. doi:10.1016/j.bjhh.2014.03.004.
9. Costa ES, Thiago LS, Otazu IB, Ornellas MH, Land MG, Orfao A. An uncommon case of childhood biphenotypic precursor-B/T acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2008;50(4):941–2. doi:10.1002/pbc.21290.
10. Naghashpour M, Lancet J, Moscinski L, Zhang L. Mixed phenotype acute leukemia with t(11;19)(q23;p13.3)/ MLL-MLLT1(ENL), B/T-lymphoid type: A first case report. *Am J Hematol*. 2010;85(6). doi:10.1002/ajh.21703.
11. Kohla SA, Sabbagh AA, Omri HE, Ibrahim F, Otazu IB, Alhajri H. Mixed Phenotype Acute Leukemia with Two Immunophenotypically Distinct B and T Blasts Populations, Double Ph+ Chromosome and Complex Karyotype: Report of an Unusual Case. *Clin Med Insights Blood Disord*. 2015;8:25–31.
12. Chauhan R, Rai P, Sharma S, Chandra J. Mixed phenotype acute leukemia: B/T-cell type-case report and review of literature. *J Appl Hematol*. 2015;6(1):27–9. doi:10.4103/1658-5127.155182.
13. Pawar RN, Banerjee S, Bramha S, Krishnan S, Bhattacharya A, Saha V. Mixed -phenotypic acute leukemia series from tertiary care center. *Indian J Pathol Microbiol*. 2017;60:43–9.
14. Gujral S, Polampalli S, Badrinath Y, Kumar A, Subramanian PG, Raje G, et al. Clinico-hematological profile in biphenotypic acute leukemia. *Indian J Cancer*. 2009;46(2):160–8. doi:10.4103/0019-509x.49156.
15. Matutes E, Pickl WF, Veer M, Morilla R, Swansbury J, Strobl H, et al. Mixed-phenotype acute leukemia: clinical and laboratory features and outcome in 100 patients defined according to the WHO 2008 classification. *Blood*. 2011;117(11):3163–71. doi:10.1182/blood-2010-10-314682.
16. Mi X, Griffin G, Lee W, Patel S, Ohgami R, Ok CY, et al. Genomic and clinical characterization of B/T mixed phenotype acute leukemia reveals recurrent features and T-ALL like mutations. *Am J Hematol*. 2018;93(11):1358–67. doi:10.1002/ajh.25256.
17. Alexander TB, Gu Z, Iacobucci I. The genetic basis and cell of origin of mixed phenotype acute leukaemia. *Nat*. 2018;562(7727):373–9.
18. Rubnitz JE, Onciu M, Pounds S, Shurtleff S, Cao X, Raimondi SC, et al. Acute mixed lineage leukemia in children: the experience of St Jude Children's Research Hospital. *Blood*. 2009;113(21):5083–9. doi:10.1182/blood-2008-10-187351.
19. Kawamoto H. Aclose developmental relationship between the lymphoid and myeloid lineages. *Trends Immunol*. 2006;27(4):169–75.
20. Vega F, Medeiros LJ, Davuluri R, Cromwell CC, Alkan S, Abruzzo LV. t(8;13)-positive Bilineal Lymphomas. *Am J Surg Pathol*. 2008;32(1):14–20. doi:10.1097/pas.0b013e31814b226e.
21. Folpe AL, Hill CE, Parham DM, Shea O, Weiss PA, W S. Immunohistochemical detection of FLI-1 protein expression: a study of 132 round cell tumors with emphasis on CD99-positive mimics of Ewing's sarcoma/primitive neuroectodermal tumor. *Am J Surg*. 2000;24(12):1657–62.
22. Lin O, Filippa DA, Teruya-Feldstein J. Immunohistochemical Evaluation of FLI-1 in Acute Lymphoblastic Lymphoma (ALL). *App Immunohistochem Mol Morphol*. 2009;17(5):409–12. doi:10.1097/pai.0b013e3181972b6d.
23. Lucas DR, Bentley G, Dan ME, Tabaczka P, Poulik JM, Mott MP. Ewing Sarcoma vs Lymphoblastic Lymphoma A Comparative Immunohistochemical Study. *Am J Clin Pathol*. 2001;115:11–7.
24. Terada T. TDT (-), KIT (+), CD34 (+), CD99 (+) precursor T lymphoblastic leukemia/lymphoma. *Int J Clin Exp Pathol*. 2012;5(2):167–70.
25. Hashimoto M, Yamashita Y, Mori N. Immunohistochemical detection of CD79a expression in precursor T cell lymphoblastic lymphoma/leukaemias. *J Pathol*. 2002;197(3):341–7. doi:10.1002/path.1126.
26. Gujral S, Ghodke K, Tembhare P, Patkar N, Subramanian PG, Arora B. A rare extramedullary and extralymphoid presentation of mixed phenotypic blastic hematolymphoid neoplasm: A study of two cases. *Indian J Med Paediatr Oncol*. 2017;38(3):394–7. doi:10.4103/ijmpo.ijmpo_94_16.

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