CASE REPORT

Aberrant expression of CD5 in a case of B acute lymphoblastic leukemia positive Philadelphia chromosome

Leucémie aigue lymphoblastique B à chromosome philadelphie positif avec expression aberrante du CD5

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Abstract

Introduction: B acute lymphoblastic leukaemia (B-ALL) is a proliferation of hematopoietic precursor cells characterized by the expression of various B-cell antigens. Expression of T cell antigens has rarely been reported in B-ALL. We report the second case CD5+ (Cluster of differentiation 5) B-ALL associated with Philadelphia chromosome (Phi+).

Observation: A 38-year old male presented with anorexia and generalized weakness for the last ten days. Hemogram revealed bicytopenia and hyperleukocytosis made of 93% difficult to classify cells. A diagnosis of diffuse large B-cell lymphoma was suspected. An immunophenotyping on peripheral blood was performed. The panel for B- cell lineage chronic lymphoproliferative disorders (B-CLPD) was used. The dim expression of CD45 and the lack of surface immunoglobuline helped to exclude a CD5 expressing mature B cell neoplasm. Then, the diagnosis of ALL was confirmed by ALL panels. Karyotype showed a Phi+. Thus, a diagnosis of B-ALL with aberrant expression of CD5 and Phi+ was established. The patient received chemotherapy according to the modified group for research on adult acute lymphoblastic leukemia philadelphia positive 2005 protocol (GRAAPH 2005). A complete remission at the end of induction was obtained. The patient received consolidation and then, hematopoietic stem cell transplantation. The patient is in complete hematological remission till the date of submission of this report.

Conclusion: Aberrant expression of CD5 associated with Phi+ has rarely been reported in B cell lineage ALL and having a poor prognosis. Pathologists and clinicians should be aware of this entity to avoid confusion with other tumors.

Keywords: Aberrant T cell antigen, immunophenotyping, Philadelphia, chromosome

Résumé

Introduction : La leucémie aiguë lymphoblastique de phénotype B (LAL-B) est une prolifération de précurseurs hématopoïétiques caractérisée par l'expression de divers antigènes de cellules B. L'expression d'antigènes de lymphocytes T a été rarement rapportée dans la LAL-B. Nous rapportons le deuxième cas de LAL-B (Cluster de différenciation 5) CD5+ associée au chromosome Philadelphie (Phi+).

Observation : Un homme âgé de 38 ans a consulté pour une anorexie et une faiblesse généralisée depuis une dizaine de jours. L'hémogramme a révélé une bicytopénie et une hyperleucocytose avec 93 % de cellules difficiles à classer. Le diagnostic de lymphome diffus à grandes cellules B a été suspecté. Un immunophénotypage sur sang périphérique a été réalisé. Le panel de syndromes lymphoprolifératifs chroniques de la lignée des cellules B (SLP-B) a été utilisé. La faible expression de CD45 et l'absence d'immunoglobuline de surface ont permis d'exclure une prolifération de cellules B matures exprimant le CD5. Ensuite, le diagnostic de LAL a été confirmé par le panel de LAL. Le caryotype montrait la présence du Phi+. Ainsi, le diagnostic de LAL-B Phi+ avec expression aberrante de CD5 a été retenu. Le patient a reçu une chimiothérapie selon le protocole modifié du groupe de recherche sur les leucémies aiguës de l'adulte philadelphie positive 2005 (GRAAPH 2005). Une rémission complète à la fin de l'induction a été obtenue. Le patient a reçu une consolidation puis une greffe de cellules souches hématopoïétiques. Le patient est en rémission hématologique complète jusqu'à la date de soumission de ce rapport.

Conclusion : Une expression aberrante de CD5 associée au Phi+ a été rarement rapportée dans la LAL-B et ayant un mauvais pronostic. Les pathologistes et les cliniciens doivent connaître cette entité pour éviter toute confusion avec d'autres tumeurs.

Mots clés : expression aberrante d'antigène de lignée T, immunophénotypage, chromosome philadelphie.

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INTRODUCTION

B acute lymphoblastic leukemia (B-ALL) is a proliferation of hematopoietic precursor cells with expression of various B-cell lineage antigens (1). The identification of aberrant markers by flow cytometry has important diagnostic and prognostic values (2). It is useful in the identification of minimal residual disease (3).

Immunophenotypic aberrancies are common in B-ALL. Coexpression of myeloid lineage markers is usual (86.5% of cases) (1). Expression of T-cell lineage markers is less common (10% of cases) (1), while the expression of the Cluster of differentiation 5 (CD5) antigen is rare (2). It may be present in as few as 2 to 4.5% of B-ALL cases (4), with one series having no CD5+ positive cases (3). The authors have performed a PubMed research (on June 17, 2022) using the combination of the following MeSH words "CD5 B-ALL and Philadelphia chromosome (Phi+)" and found 16 published cases, nly one case describing CD5 B-ALL Phi+ was reported by Ahmed et al. in 2008 (5). We report the second case of CD5+ B-ALL Phi+, according to the care guidelines (6) , with a compilation of cases previously reported in the literature.

CASE REPORT

A 38-year-old male presented with anorexia and generalized weakness for the last ten days. Physical examination revealed pallor with neither hepatomegaly nor splenomegaly.

Hemogram revealed bicytopenia [anemia (Hemoglobin =8.6 g/dL), thrombopcytopenia (Platelets count =55000/mm^3)] and hyperleukocytosis (Total Leukocyte Count =68000/mm^3) made of 93% difficult to classify cells. The cells were large in size, had a high nucleocytoplasmic ratio, basophilic and rarely vacuolated non-granular cytoplasm, a nucleus with regular outline and fine chromatin and one or more nucleoli. A diagnosis of diffuse large B-cell lymphoma was suspected.

Then, the patient was referred to our laboratory for immunophenotyping on peripheral blood. The panel for B-cell lineage chronic lymphoproliferative disorders (B-CLPD) was used: CD3, CD19, CD16, CD56, CD5, CD23, CD79b, CD20, immunoglobulins (Igs) kappa and lambda (surface).

The cells were acquired on cytometer Becton Dickinson Fluorescent Activated Cell Sorter Canto II (BD FACS Canto II) and analyzed with BD FACS Diva software. The cells with dim CD45 positivity and low side scatter (blast region) constituted 84 % of the cells. These cells were positive for CD19, CD20 (partial expression) and CD5 while negative for CD23 and CD79b as well as surface Igs.

The dim expression of CD45 and the lack of surface Ig helped to exclude a CD5- expressing mature B cell neoplasm. Then, the diagnosis of ALL was confirmed by ALL panel. Blasts were positive for CD19, CD10, cyCD79a, CD34, and human leucocyte antigen-D related (HLA-DR) while negative for myeloid markers (CD13, CD33, CD117, cytoplasmic myeloperoxidase (cyMPO) as well as lymphoid T markers (CD7, CD4, CD8, cyCD3) (Figure 1).

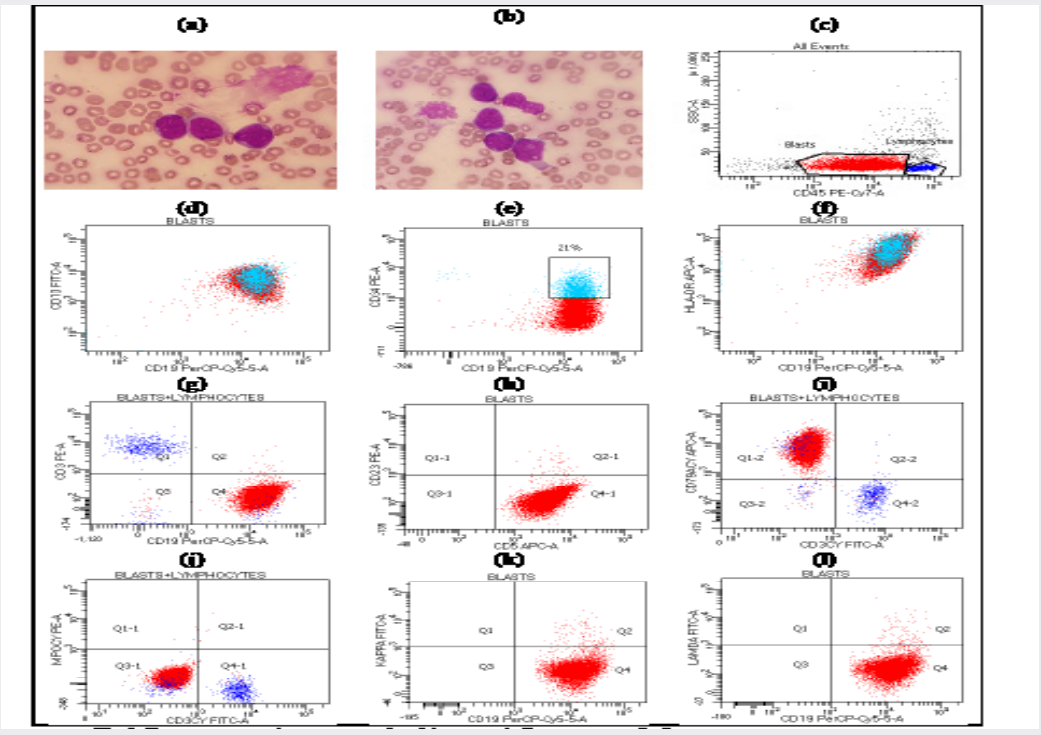

Figure 1. Bone marrow aspirate smear and multiparametric flow cytometry finding.
a.b. Bone marrow aspirate smear (x100, May Grunwald Giemsa stain). Presence of blasts which certain showed a handmirror morphology. c-l: Multiparametric flow cytometry finding performed from peripheral blood. (c): Blasts (CD45+dimand low side scatter) were gated. They showed the phenotype: CD19+/CD10+(d); CD19+/CD34+ (e); CD19+/HLADR+ (f); cytoplasmic CD79a+/ cytoplasmic CD3- (i); CD5+/ CD23- (h); CD19+/surface kappa- (k); CD19+/surface lambda- (l). These cells were also CD20+ (partial expression) and CD79b- (not shown in the figure). The blasts were negative for specific T cell markers (surface and cytoplasmic CD3 (g,i,j)) and specific myeloid marker (cytoplasmic MPO (j)). B-ALL: B acute lymphoblastic leukemia. CD: cluster of differentiation. HLA-DR: human leucocyte antigen-D related

A bone marrow aspiration was so advised. Bone marrow examination revealed cellular smears with 95% blasts with similar morphology to the peripheral blood smear. Moreover, a high proportion of blast cells showed a hand-mirror morphology characterized by a cytoplasmic tail extending out from one pole of the nucleus (Hand-mirror cells) (Figure 1). They were negative for MPO.

The Karyotype showed Phi+. The Reverse transcriptase polymerase chain reaction of bcr-abl gene was positive. Thus, a diagnosis of B-ALL with aberrant expression of CD5 and Phi+ was established.

The patient received chemotherapy according to the modified group for research on adult acute lymphoblastic leukemia philadelphia positive 2005 protocol (GRAAPH 2005) associated with the first generation of tyrosine kinase inhibitor (Cemivil®). A complete cytological and cytogenetic remission at the end of induction was obtained. The patient received consolidation and the bone marrow was in morphological remission with a major molecular response. The patient received then, hematopoietic stem cell transplantation. The patient is in complete hematological remission till the date of submission of this report (After a 20 month follow-up).

DISCUSSION

Our case illustrates an uncommon expression of CD5 on B-ALL Phi+.

Phenotypically the diagnosis of B-ALL was established in peripheral blood not in bone marrow because of the first cytological orientation in B-CLPD. Immunophenotyping based on the positivity of markers of prematurity and B lineage with expression of CD5 and then morphological examination, contributed pointing out the correct diagnosis of our case .

Several small cohort studies suggested that CD5+ B-ALL is a considerably rarer entity. Sixteen cases of B-ALL with aberrant expression of CD5 were reported until June 17, 2022. Our patient is seen as the 17 (Table 1). The medium age of this population was 18.25 years (extremes from 4 to 50 years) and the sex ratio was 8/4 (males/females). Hyperleukocytosis was present in five patients with white blood cell levels above 85000 /mm^3 in three cases. Karyotype was abnormal in 66% of cases, one of them revealed trisomy 21, the other showed t (9;22). Our patient is the second reported case of B-ALL with t(9;22).

Table 1. Summary of CD5+ B-ALL cases reported in the literature (PubMed research) (N=16).

	Case (n)	Age (years)	Sex	Adenopathy Or Organomegaly	Hemogram			Flow Cytometry	Cytogenetic
					WBC (/mm ^{3})	Hb	Platelet (/mm ^{3})	(B-ALL CD19+/CD5+)	
***Subira et al* (10)**	**1**	15	M	None	3 400	ND	ND	ND	Normal
Peterson et al (7)	**2**	16	M	ND	ND	ND	ND	CD45-/CD34+/ CD10-/ CD20-	Complex
		15	F	ND	168 000	5.1	32 000	CD45-/CD34-/ CD10+ dim/CD20+	Trisomy 22
Ahmed et al (5)	**1**	23	F	YES	26 900	7.6	67 000	CD45+dim/CD34+ CD10+/CD20+	t (9 ;22)
Seegmiller et al (1)	**4**	ND[a]	ND	ND	ND	ND	ND	ND	ND
Hussein et al (4)	**6**	17	F	ND	7 000	ND	ND	ND	Complexe
		8	M	ND	5 000	ND	ND	ND	Normal
		8	M	ND	9 000	ND	ND	ND	Complexe
		7	F	ND	2 400	ND	ND	ND	Normal
		4	M	ND	66 000	ND	ND	ND	Hypodiploid
		36	M	ND	157 000	ND	ND	ND	Abnormal
Mutreja et al (11)	**1**	20	M	Yes	3 800	ND	ND	CD34+/CD10+	sSMC*
***Sreedharanunnui et al* (2)**	**1**	50	M	Yes	85 000	7	28 000	CD34-/ CD10+/ CD20+	Normal
Our case	**1**	38	M	None	68 000	8.6	55 000	CD45+dim/CD34+/ CD10+/CD20+	t (9 ;22)

B-ALL: B acute lymphoblastic leukemia. CD: cluster of differentiation, F: Female, Hb: hemoglobin.
M: male, ND: no data; sSMC *(small supernumeray marker chromosome); PLT: Platelet; WBC: white blood cells.
α: 4 cases were 3 children and adult without detailed data.

Other hematological malignancies expressing CD5 are T-cell disorders, biphenotypic acute leukemia and typically in chronic lymphocytic leukemia or blastoid variant of mantle cell lymphoma and occasionally some other B-CLPDs: large cell B lymphoma, splenic marginal zone lymphoma, lymphoplasmacytic lymphoma, and some cases of follicular lymphoma.

In our case, T-cell disorders were excluded based on the negative expression for cyCD3, surface CD3, CD4, and CD7. On the other hand, the cells expressed CD19 and CD20 which are B lineage markers. In addition, CD10 expressed on immature B lymphocytes was detected on cells. B-CLPDs were ruled out based on morphology and phenotype: hand-mirror cells, described mostly in lymphoid malignancies, especially ALL, and expression of CD34 and CD10, dim expression of CD45 and lack of surface Igs.

In addition to the rarity of aberrant expression of CD5 on B-ALL, the available literature suggests this to be associated with an overall poor prognosis (2). Peterson et al. (7) described the poor prognosis of this variant of ALL. However, the small number of reported CD5 + B-ALL cases makes it difficult to draw a conclusion about the natural behavior of malignancy with this phenotype. In our patient also, expression of CD5 was associated with other poor prognostic factors like age (38 years), high total leukocyte count (68000/mm3), expression of CD20 and Phi + which is implicated in cell proliferation and leukemogenesis (8). Although CD10+ subgroup of B-ALL has a favorable prognosis, adults and children with Phi+ have an unfavorable prognosis (9).

Though our patient had responded to chemotherapy and had phenoidentical allogeneic stem cell transplantations; the prognosis will be clear only on long-term follow-up.

CONCLUSION

The purpose of this reported case is to create awareness of atypical morphology as B-CLPD and to emphasize that aberrant expression of CD5 does not exclude the diagnosis of B-ALL, although it is rare. Thus, careful morphological evaluation and immunophenotyping are important for a correct diagnosis.

Additional research is required to determine whether CD 5+ B-ALL Phi+ represents a uniquely aggressive subcategory of B-ALL.

REFERENCES

1. Seegmiller AC, Kroft SH, Karandikar NJ, McKenna RW. Characterization of Immunophenotypic Aberrancies in 200 Cases of B Acute Lymphoblastic Leukemia. Am J Clin Pathol. 2009 ;132:940–9.
2. Sreedharanunni S, Kumar N, Khadwal A. CD5 Positive B Lymphoblastic Leukemia: Report of a Case with Review of Literature. Indian J Hematol Blood Transfus. 2016 ;32(S1):1–4.
3. Jalal SD, Al-Allawi NAS, Al Doski AAS. Immunophenotypic aberrancies in acute lymphoblastic leukemia from 282 Iraqi patients. Int J Lab Hematol. 2017 ;39:625–32.
4. Hussein S, Gill KZ, Sireci AN, Colovai AI, Small T, Emmons FN, et al. Aberrant T-cell antigen expression in B lymphoblastic leukaemia: T Antigen Expression in B Lymphoblastic Leukaemia. Br J Haematol. 2011 ;155:449–56.
5. Ahmed D, Ahmed TA, Ahmed S, Tipu HN, Wiqar MA. CD5-positive acute lymphoblastic leukemia. J Coll Physicians Surg--Pak JCPSP. 2008 ;18:310–1.
6. Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D, et al. The CARE guidelines: consensus-based clinical case reporting guideline development. J Med Case Reports. 2013 ;7:223.
7. Peterson MR, Noskoviak KJ, Newbury R. CD5-Positive B-Cell Acute Lymphoblastic Leukemia. Pediatr Dev Pathol. 2007 ;10:41–5.
8. Jennings CD, Foon KA. Recent advances in flow cytometry: application to the diagnosis of hematologic malignancy. Blood. 1997 ;90:2863–92.
9. Gökbuget N, Hoelzer D. Treatment of Adult Acute Lymphoblastic Leukemia. Hematology. 2006 ;2006:133–41.
10. Subira´ D, Roman A, Jime´nez-Garo´fano C, Prieto E, Martı´nezDelgado B, Aceituno E et al. CD19/CD5 acute lymphoblastic leukemia. Med Pediatr Oncol. 1998;31:551–2.
11. Mutreja D, Pati HP, Bansal D, Sharma RK, Jain S. Aberrant Immunophenotypic Expression of CD5 in a Case of B Acute Lymphoblastic Leukemia: A Case Report. Indian J Hematol Blood Transfus. 2014 ;30(S1):212–4.