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COEXISTENCE OF PHILADELPHIA CHROMOSOME IN ACUTE PROMYELOCYTIC LEUKAEMIA: TWO RARE CASES, WITH A LITERATURE REVIEW

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ABSTRACT

Background: Acute promyelocytic leukaemia (APL) is characterised by the t(15;17)/PML::RARA translocation and typically responds favourably to differentiating agents such as all-trans retinoic acid (ATRA). The coexistence of APL with the Philadelphia chromosome (t(9;22)/BCR::ABL1), a hallmark of chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL), is extremely rare and carries uncertain prognostic and therapeutic implications.

Case description: We describe two cases where these studies confirmed APL with t(15;17)(q22;q21), in addition to t(9;22)(q34;q11), consistent with dual cytogenetic abnormalities. The patient was initiated on induction therapy with ATRA in combination with idarubicin, resulting in rapid haematologic remission by day 15, with normalisation of blood counts and significant clinical improvement.

Conclusion: These cases highlight the diagnostic and therapeutic challenges posed by APL with concurrent BCR::ABL1 rearrangement. While the PML::RARA clone responded robustly to ATRA-based therapy, the persistence of BCR::ABL1 warrants consideration of tyrosine kinase inhibitor (TKI) therapy and close molecular monitoring. Our report contributes to the limited body of literature on this rare dual-driver leukaemia and underscores the need for individualised, biology-driven management strategies.

KEYWORDS

Acute promyelocytic leukaemia, Philadelphia chromosome, PML-RARA

LEARNING POINTS

- The rare genetic co-occurrence of t(15;17)/PML::RARA and t(9;22)/BCR::ABL1 translocations may be identified in a single patient with acute promyelocytic leukaemia (APL).
- Successful induction using all-trans retinoic acid (ATRA) together with imatinib achieved effective control of both leukemic clones.
- The patient demonstrated rapid haematologic remission and favourable clinical recovery, suggesting a positive outcome with this therapeutic approach.

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INTRODUCTION

The t(9;22)(q34;q11) chromosome translocation, resulting in the BCR-ABL1 fusion oncoprotein, is a well-established hallmark of chronic myeloid leukaemia (CML), being present in more than 95% of cases[1]. Beyond CML, this translocation is also observed in approximately 10–20% of adults and 2–5% of children with acute lymphoblastic leukaemia (ALL) and in rare instances – approximately 1% of cases – in acute myeloid leukaemia (AML)[2]. The presence of BCR-ABL1 in AML is associated with an adverse prognosis, resistance to conventional therapy, and poses unique therapeutic challenges given the potential role of tyrosine kinase inhibitors (TKIs) in disease management[2].

Acute promyelocytic leukaemia (APL) represents a biologically distinct and clinically unique subtype of AML. It is characterised by translocations involving the retinoic acid receptor alpha (RARα) gene on chromosome 17[3]. In over 95% of cases, the defining lesion is t(15;17)(q22;q21), which generates the PML-RARα fusion gene, conferring responsiveness to all-trans retinoic acid (ATRA) and arsenic trioxide (ATO), a therapeutic revolution that has transformed APL from a highly fatal to a highly curable disease. Variant translocations involving RARα, such as t(11;17) and t(5;17), are rare but clinically significant, often conferring altered therapeutic responses[4].

The coexistence of t(15;17) and t(9;22) within the same leukaemic clone is exceptionally rare and represents a distinct diagnostic and therapeutic dilemma. Cytogenetic studies have documented occasional cases of APL with concurrent BCR-ABL1 positivity, suggesting either a true de novo APL with dual genetic lesions or a therapy-related clonal evolution[4-11]. Importantly, the prognostic implications of such dual rearrangements remain uncertain, though published reports consistently describe an adverse clinical course, with resistance to standard ATRA/ATO-based regimens and a need for incorporation of TKI therapy[6].

In our cases, cytogenetic analysis demonstrated a complex karyotype, including the classical t(15;17)(q22;q21), in addition to t(9;22)(q34;q11), trisomy 8 and t(9;14)(q10;q10). The t(15;17) translocation was detected in 70% of metaphases, consistent with de novo APL, whereas the t(9;22) translocation was identified in 20%, raising the possibility of clonal heterogeneity. This highlights the diagnostic challenges, therapeutic implications and review of the available literature on this rare but clinically significant cytogenetic association.

CASE DESCRIPTION

Case 1: A 70-year-old male presented to the haematology clinic with chief complaints of progressive fatigue, accompanied by generalised weakness and dysphagia, persisting and gradually worsening over the preceding three months. Prior to haematologic assessment, the patient was referred to dermatology for evaluation of macroglossia, as illustrated in *Figure 1*. Histopathological examination of a tongue biopsy demonstrated non-caseating granulomatous infiltration,



Figure 1. This image illustrates the presence of macroglossia, a prominent clinical feature in this patient.

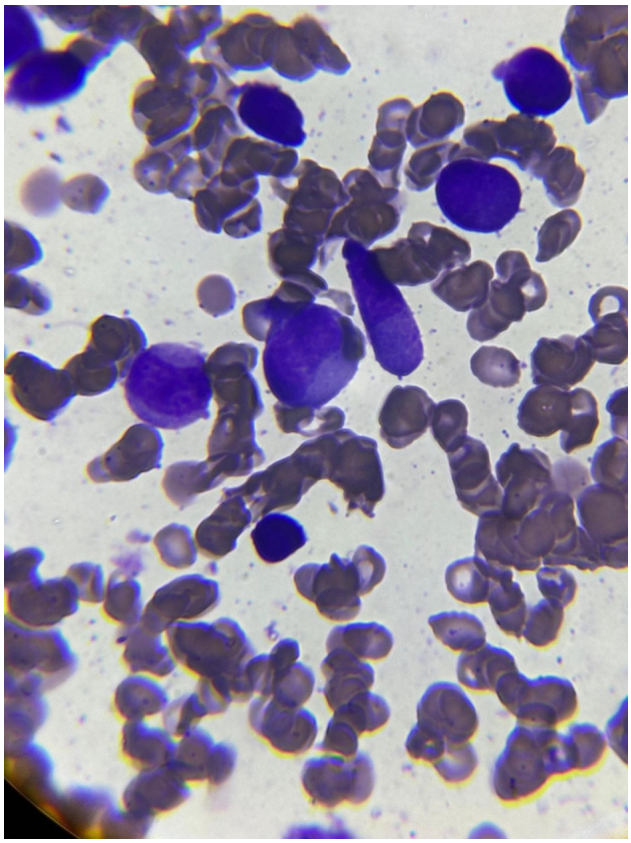


Figure 2. Bone marrow aspirate demonstrated infiltration with abnormal promyelocytes characterised by numerous coarse cytoplasmic granules.

raising concern for possible systemic involvement. Further history revealed a significant weight loss of approximately 10 kg over two months. Physical examination was notable for pallor; however, there was no clinical evidence of lymphadenopathy or hepatosplenomegaly.

Initial laboratory investigations demonstrated profound pancytopenia: white blood cell count was 1.2 $\times 10^3$/µl, haemoglobin was critically reduced at 4.5 g/dl and platelet count was 20 $\times 10^9$/l. Inflammatory markers were elevated, with an erythrocyte sedimentation rate of 60 mm/h. Biochemical studies showed markedly elevated serum vitamin B12 (12,000 pg/ml) and folate within the normal range (5 ng/ml). Iron studies revealed serum iron of 63 µg/dl, total iron-binding capacity of 224 µg/dl and ferritin of 400 ng/ml, consistent with anaemia of chronic disease. Lactate dehydrogenase was elevated at 524 U/l, uric acid was mildly increased at 8 mg/dl and creatinine was 1 mg/dl. The coagulation profile demonstrated a prothrombin time of 60%, international normalised ratio of 1.2, activated partial thromboplastin time of 40 seconds and a fibrinogen level of 170 mg/dl. A contrast-enhanced CT scan was performed to exclude an underlying solid tumour or sarcoma and was unremarkable.

A peripheral blood smear demonstrated a predominance of immature myeloid cells, including myeloblasts and promyelocytes. Bone marrow aspiration revealed a hypercellular marrow with 80% blast infiltration, as shown in *Figure 2*. Immunophenotyping via flow cytometry identified blasts expressing CD117, CD34, CD33, CD13 and myeloperoxidase, with low HLA-DR expression (5%) – a profile highly suggestive of APL.

Cytogenetic analysis revealed a complex karyotype. The hallmark translocation t(15;17)(q24;q21), characteristic of APL, was present in 70% of analysed metaphases. Additionally, t(9;22)(q34;q11) was identified in 20% of cells as shown in *Figure 3*. Fluorescence in situ hybridisation analysis revealed a 15;17 translocation with 70% positivity and a 19;22 translocation with 30% positivity.

This dual cytogenetic abnormality placed the patient in a low-risk category per European LeukemiaNet (ELN) guidelines, despite his low initial leukocyte and platelet counts.

The patient was diagnosed with APL with concurrent Philadelphia chromosome positivity and was promptly initiated on induction therapy with ATRA at a dose of 45 mg/m^2 daily for 45 days, in combination with idarubicin 60 mg/m^2 administered on days 2, 4, 6 and 8. Subsequently, imatinib 400 mg once daily was introduced.

Remarkably, by day 15 of treatment, the patient achieved complete haematologic remission, as evidenced by normalisation of peripheral blood counts and notable clinical improvement, including resolution of dysphagia and restoration of baseline energy levels.

At six months follow-up, the patient maintained clinical and haematologic remission with haemoglobin 10.5 g/dl, platelet count 200 $\times 10^9$/l and white blood cell count 5 $\times 10^9$/l. Molecular testing revealed minimal residual disease with a BCR-ABL transcript level of 0.1% and a PML-RARA level of 1%.

Case 2: A 40-year-old woman presented with severe genital bleeding following a second-trimester miscarriage. Initial laboratory evaluation revealed pancytopenia, prompting referral to the haematology clinic for further assessment.

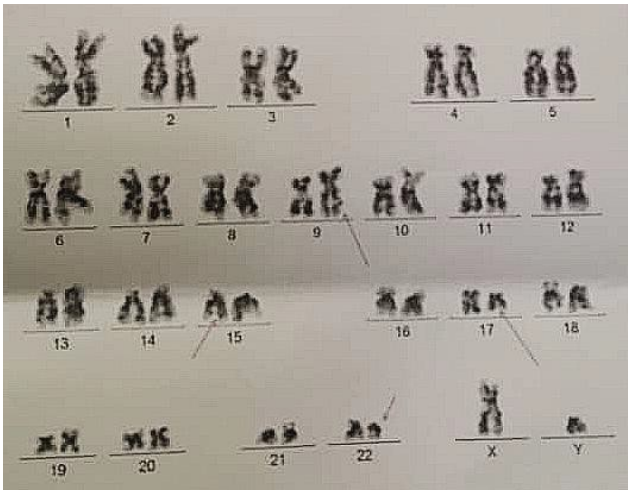


Figure 3. Karyotype for the patient showed 46,XY t(15;17) 70% and t (9;22) 20%.

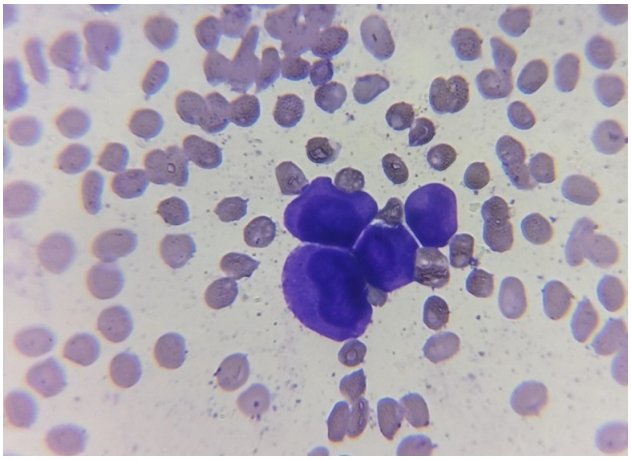


Figure 4. Blood smear showed abnormal promyelocytes (×100 wright stain).

On examination, the patient had multiple ecchymoses, but no lymphadenopathy or hepatosplenomegaly was detected. Laboratory investigations demonstrated a white blood cell count of 10 $\times 10^9$/l, haemoglobin 6 g/dl, platelets 20 $\times 10^9$/l, uric acid 4 mg/dL, fibrinogen 145 mg/dL, LDH 554 U/l and serum creatinine 0.7 mg/dl. The coagulation profile was normal. Abdominal ultrasound and chest radiography were unremarkable.

A peripheral blood smear revealed 86% blasts with large nuclei and prominent azurophilic granulation indicating promyelocyte cells as shown in *Figure 4*. Bone marrow aspiration confirmed 70% infiltration by abnormal promyelocytes. Flow cytometric immunophenotyping demonstrated positivity for CD45, CD117, CD33, CD34 and myeloperoxidase, while HLA-DR, CD14, CD64 and CD79a were negative. Cytogenetic analysis identified a complex karyotype: 46,XX, t(15;17) and t(9;22). Molecular testing by PCR confirmed the presence of the PML::RARA fusion transcript.

A diagnosis of low-risk APL was established. The patient was initiated on induction therapy with ATRA combined with daunorubicin (days 2, 4, 6 and 8), along with the addition

of imatinib 400 mg once daily to target the concurrent BCR::ABL1 rearrangement.

She achieved haematologic stabilisation following induction and subsequently received consolidation therapy per APL protocols, with ATRA and imatinib maintenance according to international guidelines.

At present, after four years of follow-up, the patient remains in complete clinical and molecular remission. Molecular monitoring has consistently demonstrated negative PML::RARA and negative BCR::ABL1 transcripts, confirming sustained remission. Her current blood counts remain within normal limits (white blood cell count 4.5 $\times 10^9$/l, haemoglobin 11 g/dl, platelets 150 $\times 10^9$/l), and she is in good general health.

DISCUSSION

Philadelphia chromosome-positive acute myeloid leukaemia (Ph+ AML) is an uncommon entity, with a reported incidence ranging from 0.5 to 3% of AML cases, and is generally associated with an adverse prognosis and poor response to standard AML therapies[9]. The presence of the BCR::ABL1 fusion gene is most commonly linked to CML and, less frequently, to ALL and de novo AML[2]. Rare cases of Ph^+ AML harbour additional cytogenetic aberrations, including inv(16), t(8;21)/RUNX1-RUNX1T1, inv(3), deletion of 5q and NPM1 mutations; concomitant t(15;17)/PML-RARA – the defining lesion of APL – is exceedingly rare[5,6,8].

In the literature, such cases remain exceptional: 17 reported in CML (including one following chronic myelomonocytic leukaemia), 1 in acute basophilic leukaemia, 5 in AML (3 de novo and 2 secondary to chronic myelomonocytic leukaemia and myelofibrosis, respectively), and 1 in ALL[5,9]. To date, only five patients with concurrent BCR::ABL1 and PML::RARA rearrangements have been documented[4,6].

Our patient had no prior haematologic history, and laboratory investigations revealed no evidence suggestive of CML (e.g. splenomegaly or basophilia), supporting the diagnosis of de novo APL with coexistent BCR::ABL1 fusion.

Only a limited number of cases with concurrent PML::RARA and BCR::ABL1 rearrangements have been described in the literature[5], and reported outcomes have been heterogeneous. In one instance, the patient received induction with ATRA and arsenic trioxide (ATO) but died from an intracranial haemorrhage shortly after treatment initiation[6]. Conversely, another report described successful induction with ATRA monotherapy, which resulted in haematologic remission; however, the PML::RARA fusion persisted, while BCR::ABL1 became undetectable post-induction[6]. These observations highlight the clinical challenges and biological complexity associated with dual-driver leukaemias, emphasising the need for individualised therapeutic strategies.

The prognostic and therapeutic implications of coexistent cytogenetic abnormalities such as PML::RARA and BCR::ABL1 remain poorly defined. The PML::RARA fusion gene confers sensitivity to differentiating agents, including ATRA and ATO, which have revolutionised the management of APL and markedly improved survival outcomes. In contrast, TKIs represent the most successful class of targeted agents for CML; however, their benefit in Ph^+ AML has been inconsistent and generally limited. Current evidence suggests that single-agent TKI therapy is insufficient to achieve durable disease control in Ph^+ AML, and thus TKIs are not routinely recommended as part of first-line treatment. Nevertheless, their use as salvage therapy, particularly in combination with other agents, remains a reasonable strategy[3].

In our patient – initially classified as low-risk APL – induction with ATRA plus idarubicin resulted in a rapid haematologic remission by day 15, underscoring the dominant role of the PML::RARA clone at presentation. However, persistence of a BCR::ABL1-positive subclone poses an ongoing risk of relapse. Published cases suggest that incorporating a TKI (e.g. imatinib, dasatinib or ponatinib) may be necessary to achieve molecular remission and eradicate the BCR::ABL1 clone[11]. In line with this evidence, the addition of imatinib to our patient's treatment regimen resulted in favourable outcomes, with sustained haematologic and molecular remission. Furthermore, given the adverse risk conferred by complex cytogenetics, consolidation with allogeneic haematopoietic stem cell transplantation should be strongly considered in eligible patients.

The prognostic significance of t(9;22) in APL remains uncertain. While additional cytogenetic abnormalities generally do not alter the favourable prognosis of APL, this principle has not been systematically evaluated in cases with concurrent t(9;22). Notably, Mao et al.[5] reported a dual-translocation case treated with ATRA, ATO and imatinib; although remission was achieved, the specific contribution of imatinib remained unclear[6]. Given the extreme rarity of simultaneous PML::RARA and BCR::ABL1 rearrangements, evidence-based guidelines for optimal management are lacking, and treatment must be individualised.

These cases exemplify the feasibility of concurrently targeting both molecular drivers. As the landscape of AML mutational profiling expands and novel targeted therapies emerge, discerning the biological hierarchy and clinical relevance of each lesion will be critical. In particular, distinguishing between primary 'driver' mutations requiring treatment and secondary or 'bystander' alterations with limited clinical impact may help optimise therapeutic efficacy while minimising toxicity. Future clinical studies will be essential to inform treatment strategies for complex, multi-aberration leukaemias.

CONCLUSION

APL with concurrent BCR-ABL1 translocation represents a rare and biologically complex entity at the intersection of two distinct leukaemias. Our cases demonstrate that the PML::RARA-driven clone may initially dominate the clinical presentation and remain highly sensitive to ATRA-based therapy, resulting in rapid haematologic remission. However,

the persistence of a BCR::ABL1-positive subclone poses a risk of relapse and therapeutic resistance, highlighting the importance of incorporating TKI therapy and considering allogeneic haematopoietic stem cell transplantation in eligible patients. This case reinforces the necessity of comprehensive cytogenetic and molecular testing in all patients with acute leukaemia, as rare dual rearrangements may critically influence both prognosis and treatment decisions.

REFERENCES

1. Carter BZ, Mak DH, Cortes J, Andreeff M. The elusive chronic myeloid leukemia stem cell: does it matter and how do we eliminate it? *Semin Hematol* 2010;**47**:362–370. doi: 10.1053/j.seminhematol.2010.06.006
2. Hochhaus A, Reiter A, Skladny H, Melo JV, Sick C, Berger U, et al. A novel BCR-ABL fusion gene (e6a2) in a patient with Philadelphia chromosome-negative chronic myelogenous leukemia. *Blood* 1996;**88**:2236–2240.
3. Mistry AR, Pedersen EW, Solomon E, Grimwade D. The molecular pathogenesis of acute promyelocytic leukaemia: implications for the clinical management of the disease. *Blood Rev* 2003;**17**:71–97. doi: 10.1016/s0268-960x(02)00075-9
4. Sun X, He Y, Mao C, Zhu L, Qin X, Huang S. BCR/ABL fusion gene detected in acute promyelocytic leukemia: a case study of clinical and laboratory results. *Leuk Lymphoma* 2014;**55**:435–438. doi: 10.3109/10428194.2013.800870
5. Mao L, Wang H, Cheng Y, Wang Y, Chen Z, Jin J. Occurrence of t(15;17)(q22;q21) and t(9;22)(q34;q11) in a patient with acute promyelocytic leukemia. *Leuk Lymphoma* 2009;**50**:466–470. doi: 10.1080/10428190802676728
6. Takahashi H, Sakai R, Hattori Y, Ohshima R, Hagihara M, Kuwabara H, et al. [Biclonal co-existence of t(15;17) and t(9;22) chromosomal abnormalities in acute promyelocytic leukemia.] *Rinsho Ketsueki* 2011;**52**:37–40. Chinese.
7. Preudhomme C, Lai JL, Plantier I, Demory JL, Zandecki M, Fenaux P. Cytogenetic and molecular remission in a case of acute myeloid leukaemia (AML) with inversion of chromosome 16 (Inv(16)) and Philadelphia chromosome (Ph). *Br J Haematol* 1992;**82**:623–626. doi: 10.1111/j.1365-2141.1992.tb06480.x
8. Siddiqui AD, Sheikh ZS, Liu D, Seiter K. Coexistence of inversion 16 and the Philadelphia chromosome in patients with acute myelogenous leukemia. *Leuk Lymphoma* 2002;**43**:1137–1140. doi: 10.1080/10428190290021434
9. Li YS, Hayhoe FG. Ph1 chromosome positive acute myelomonocytic leukaemia with inverted chromosome 16. *Br J Haematol* 1988;**69**:576. doi: 10.1111/j.1365-2141.1988.tb02422.x
10. Wu Y, Slovak ML, Snyder DS, Arber DA. Coexistence of inversion 16 and the Philadelphia chromosome in acute and chronic myeloid leukemias: report of six cases and review of literature. *Am J Clin Pathol* 2006;**125**:260–266. doi: 10.1309/F0MX-5CL8-CEDY-3W86
11. Zhang LJ, Gan YM, Yu L. Occurrence of BCR/ABL fusion gene in a patient with acute promyelocytic leukemia. *Med Oncol* 2015;**32**:382. doi: 10.1007/s12032-014-0382-0