
An Isodicentric (X)(q13) abnormality- A chromosomal abnormality

Case report

Tay Za Kyaw¹, Kok-Siong Chen², Josephine Pasangna³, Ping Chong Bee⁴

¹ Pathology Department, Hospital Raja Permaisuri Bainun, Ipoh.

² Cancer Research Institute, University Malaya.

³ Department of Pathology, Faculty of Medicine, University Malaya.

⁴ Department of Medicine, Faculty of Medicine, University Malaya.

ABSTRACT

Recurring chromosomal abnormalities are involved in the pathogenesis of hematologic malignancies and are important indicators for diagnosis and prognosis. An isodicentric X chromosome with breakpoints in Xq13 [idic(X) (q13)] is a rare but recurrent abnormality in myeloid malignancies.

This chromosomal anomaly has been demonstrated exclusively in females, typically of advanced age. The fact that idic(X) (q13) often occurs as the sole cytogenetic abnormality suggests that it may itself be sufficient for leukemogenesis. However, the pathogenetic outcome of this chromosomal anomaly remains unknown. Herein we describe a patient presented with left abdominal discomfort due to underlying massive splenomegaly. Peripheral blood smear and bone marrow biopsy findings were consistent with underlying myeloproliferative/myelodysplastic neoplasm.

Cytogenetic test showed the presence of isodicentric (X)(q13). Molecular assessment for BCR-ABL and JAK2 mutational study were negative. Patient is treated with hydroxyurea, thalidomide and prednisolone. There was no sibling available for transplant. Her clinical condition worsened over the past year with the increasing usage of blood components together with the progression of total white cells count and blast cells count.

Key words: Idic(X)(q13), Isodicentric X chromosome, Myelodysplastic Syndromes

Corresponding author address:

Kyaw Tay Za:

Pathology Department, Hospital Raja Permaisuri Bainun, 30990 Ipoh, Perak State, Malaysia.

Ph: +60-5-2085269, Fax: +60-5-2423790

Email: kyawtayza79@gmail.com

Conflict of interest: No conflict of interest.

Case report is original: Yes

Whether case report published elsewhere in other journal? No

INTRODUCTION

Recurring chromosomal abnormalities are involved in the pathogenesis of hematologic malignancies and are important indicators for diagnosis and prognosis.¹ An isodicentric X chromosome with breakpoints in Xq13 [idic(X)(q13)] is a rare but recurrent abnormality in myeloid malignancies with approximately 30 cases reported in the literature to date.² Most cases are myelodysplastic syndromes but cases of other myeloid malignancies such as acute myeloid leukemia, primary myelofibrosis, atypical chronic myeloid leukemia and chronic myelomonocytic leukemia were also reported.^{2,3,4} Herein we describe a case of myelodysplastic/myeloproliferative neoplasm with idic(X)(q13) abnormality.

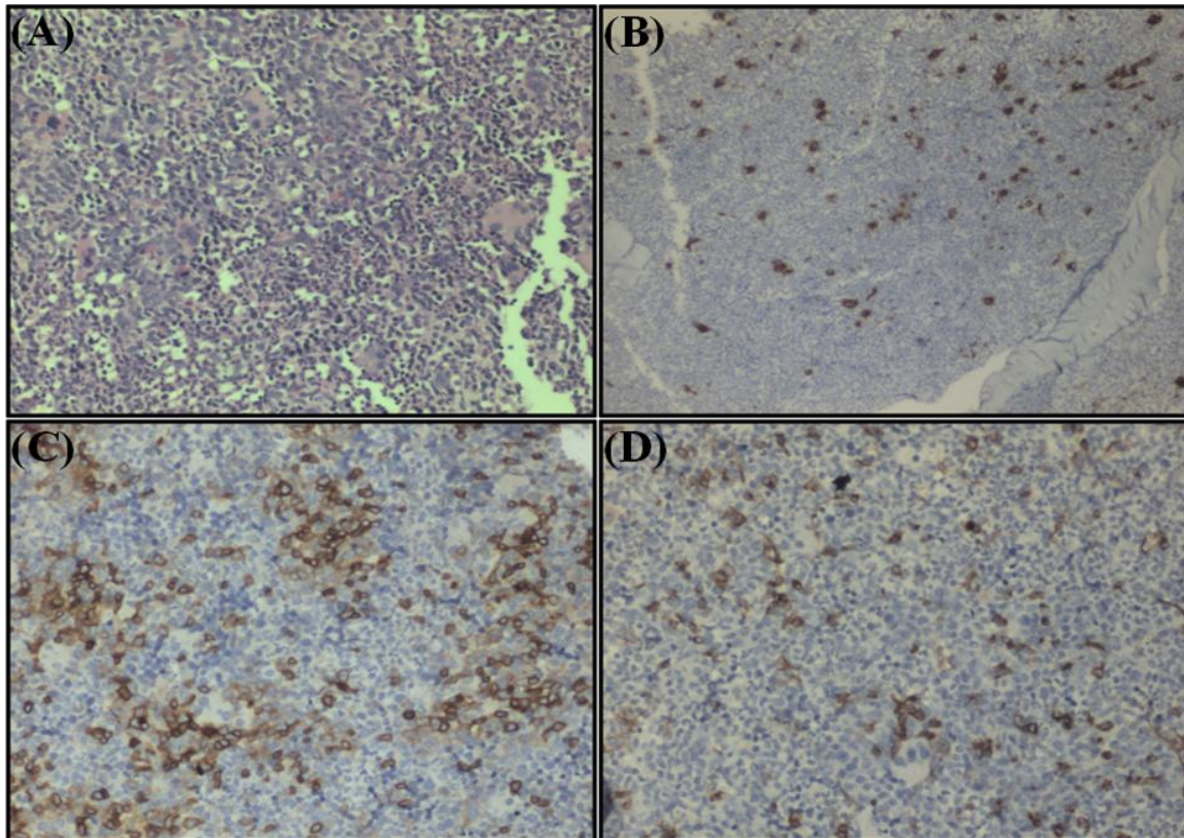
CASE REPORT

A 44-year-old Indonesian lady was presented with a complaint of left abdominal discomfort. A massive splenomegaly was detected on examination. Her full blood count on

admission showed hemoglobin of 78 g/L, white cell count of $43.2 \times 10^9/L$ and platelet count of $242 \times 10^9/L$. Peripheral blood smear exhibited a leucoerythroblastic picture with neutrophilia and monocytosis. Some dysplastic neutrophils and occasional blasts were noted. Bone marrow aspiration (BMA) was suboptimal.

Bone marrow biopsy showed a hypercellular marrow with increase in granulopoiesis and megakaryopoiesis. The abnormally localized clusters of immature precursor cells and dysplastic megakaryocytes including micromegakaryocytes and hypolobulated forms were noted. These immature precursor cells were CD117+, CD34+ (in a small proportion) and CD68-. Immunohistochemical staining using CD61 recognize the increase numbers of megakaryocytes (Figure 1A, B, C and D).

Figure 1: (A): Hypercellular marrow with abnormally localized clusters of immature precursor cells (H&E, x40) (B): CD61 staining recognize the increase in megakaryopoiesis and presence of dysplastic megakaryocytes. (C&D): Abnormally localized immature precursor cells are CD117+ and CD34+ (in a small proportion).



There was a mild increase in reticulin fibres. Molecular assessment for BCR-ABL transcripts and JAK2 mutational study were negative. Chromosomal analysis of bone marrow sample revealed 46,XX,idic(X)(q13) karyotype in 10 out of 20 cells analysed (Figure 2). In view of the morphological, immunohistochemical and molecular findings, the diagnosis of

myelodysplastic/myeloproliferative neoplasm (unclassifiable) was made.

The patient was treated with hydroxyurea, thalidomide and prednisolone. Considering the relatively young age of the patient, allogeneic bone marrow transplantation was suggested. However, there was no sibling available for transplant. Her clinical conditions worsened over the past year with the increasing usage of blood components. The

full blood count in the last follow-up showed hemoglobin of 67 g/L, white cell

count of $64.5 \times 10^9/L$ and platelet count of $135 \times 10^9/L$ with 5% blast cells.

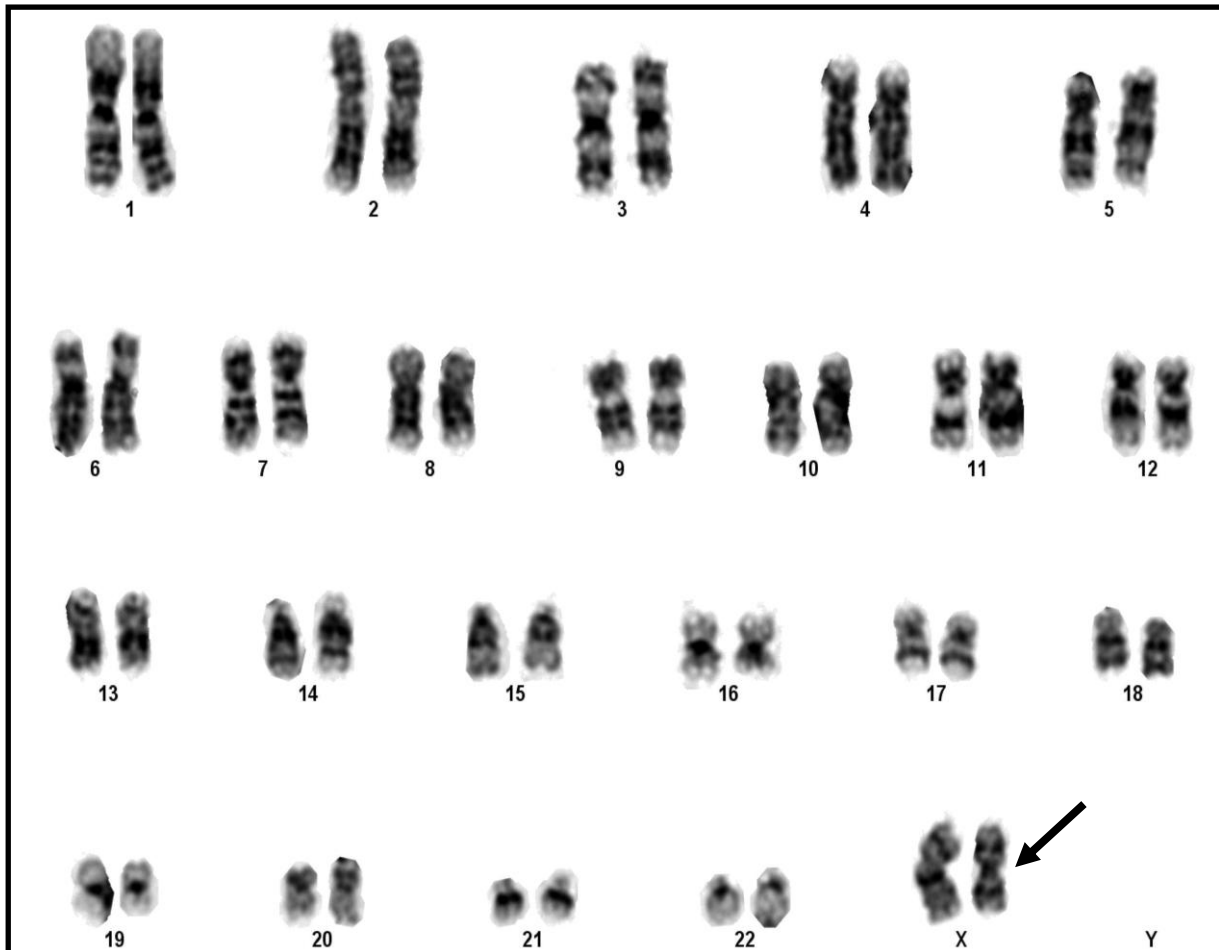


Figure 2: The full karyogram of bone marrow cells showing 46,XX,idic(X)(q13) [Arrow]

DISCUSSION

Idic(X)(q13) anomaly was first reported by Dewald et al in three cases of acquired sideroblastic anemia.⁵ This chromosomal anomaly has been demonstrated exclusively in females, presumably because the formation of idic(X)(q13) would result in nullisomy for Xq13-qter in males, which would be lethal

for the cells. The median age of patients reported at the time of diagnosis was 73.5 years. Ring sideroblasts were frequently detected in these cases due to the possible loss of *ABCB7* gene which is localised in deleted region.² In our case, the presence of ring sideroblasts cannot be assessed accurately because of the suboptimal BMA.

The fact that idic(X)(q13) often occurs as the sole cytogenetic abnormality suggests that it may itself be sufficient for leukemogenesis. The exact pathogenetic outcome of this chromosomal anomaly remains unknown; formation of a fusion gene, deregulation of a gene close to the breakpoint or dosage effects resulting from the concurrent gain of Xpter-q13 and loss of Xq13-qter are equally possible.²

In a SNP array study of 14 cases of idic(X)-positive myeloid malignancies by Paulsson et al², the authors detected a total of 11 break points. However, none of these breakpoints occur in a gene, strongly indicating that idic(X)(q13) does not cause a formation of fusion gene. Instead, the dosage effects from the concurrent gain of Xpter-q13 and loss of Xq13-qter could be the most likely functional outcome. It was also reported in the same study that additional genetic abnormalities were present in the majority of idic(X)-positive malignancies with TET2 mutation being the most common secondary event.²

The outcome of idic(X)-positive cases is variable; some investigators report aggressive and rapidly fatal disease and others a relatively favorable clinical

course, with survival of several years despite the generally advanced age of patients.² As for our patient, her clinical condition worsened significantly over the past year with the increasing requirement of blood components together with the progression of total white cells count and blast cells count.

CONCLUSION

In conclusion, although the isodicentric (X)(q13) is a relatively rare cytogenetic abnormality with only few cases reported so far, the possibility of such anomaly should be kept in mind during the cytogenetic analysis particularly in female patients with myeloid malignancies. Further studies are required in better understanding of the exact pathogenesis of idic(X)-positive malignancies as well as the role of additional genetic abnormalities such as TET2 mutation.

REFERENCES

1. Gorczyca W. Cytogenetics, FISH and molecular testing in hematologic malignancies. 1st ed. United Kingdom: Informa Healthcare, 2008.
2. Paulsson K, Haferlach C, Fonatsch C, Hagemeyer A, Andersen MK, Slovak ML and Johansson B (on behalf of the MDS foundation). The idic(X)(q13) in myeloid malignancies: breakpoint clustering in segmental duplications and association with TET2 mutations. *Human Molecular Genetics* 2010;19:1507-1514.
3. Temperani P, Zucchini P, Emilia G, Sacchi S, Selleri L and Torelli U. Isodicentric X chromosome in myeloproliferative disorders. *Acta Haematol* 1989;81:152-154.
4. Oscier DG. Atypical chronic myeloid leukaemia, a distinct clinical entity related to the myelodysplastic syndrome? *Br J Haematol* 1996;92:582–586.
5. Dewald GW, Pierre RV and Phyllyk RL. Three patients with structurally abnormal X chromosomes, each with Xq13 breakpoints and a history of idiopathic acquired sideroblastic anemia. *Blood* 1982;59:100–105.