Asmida I, Goh A S, Moses E.J, Chew T K, Narazah M Y

[1]Advanced Medical and Dental Institute, Universiti Sains Malaysia, No 6 (Lot 13), Persiaran Seksyen 4/9, Bandar Putra Bertam, 13200 Kepala Batas, [2]Haematology Unit, Hospital, Pulau Pinang, Jalan Residensi, 10990 Pulau Pinang, Malaysia.

(Received 9th December 2013. Revised 12th December 2013. Accepted. Published *Online* 24th December 2013.)

Correspondence: Narazah Mohd Yusoff
Email: narazah@amdi.usm.edu.my

Trisomy 11 In an Elderly Man With Myelodysplastic Syndrome – A Case Report and Review of the Literature

We report a case of a 78 year old man diagnosed with myelodysplastic syndrome (MDS) with trisomy 11 and peripheral pancytopaenia. The conventional karyotyping using G-banding technique of the lymphocytes showed 47,XY,+11 with an additional chromosome 11. The analysis demonstrated trisomy 11 in 13 out of 14 metaphases examined. To the best of our knowledge, this is the first report of a patient with MDS with trisomy 11 in Malaysia.

Keywords: myelodysplastic syndrome, cytogenetic analysis, trisomy 11, karyotype, pancytopaenia

INTRODUCTION

Myelodysplastic syndrome (MDS) is frequently associated with many chromosomal abnormalities such as del 5q, monosomy 7, trisomy 8, del 20q and –Y (Martínez-Ramírez *et al*., 2008; Pozdnyakova *et al*., 2008; Romeo *et al*., 2002; Sendi *et al*., 2002). However, MDS with trisomy 11 have been reported in only few occasions (Kojima *et al*., 2002; List *et al*., 1997; Ohyashiki *et al*., 1989; Tanabe *et al*., 1990; Yamamoto *et al*., 1997). In the International Prognostic Scoring System (IPSS), it is assigned under the intermediate-risk group with undefined clinical significance and is not associated with any French-American-British (FAB) classification. It is observed that, MDS patients with trisomy 11 have a shorter overall survival rate and represent an early evolving stage of acute myeloid leukemia (AML) (Wang *et al*., 2010). Here we report a case of an elderly man with MDS associated with trisomy 11.

CASE REPORT

A 78-year-old male who works as a street hawker with a past medical history of hypertension, haemorrhoids and gastritis, was admitted with pancytopaenia in May 2011. The patient had undergone oesophago-gastric-duodeno-scopy (OGDS) in 1998 and haemorrhoid banding ligation in 2008. He was prescribed with iron tablets for a year by the general practitioner. The patient complained of intermittent giddiness for a year, associated with shortness of breath on exertion and claimed to have blackish stool in May 2011. He did not have any bleeding tendency. There was no loss of weight or appetite. There was no other significant drug history. He received three units of platelet transfusion since May 2011. He is a non-smoker and does not consume alcohol.

On examination, the patient was alert, conscious, not tachypnoeic, and vital signs were normal. Physical examination was unremarkable apart from mild pallor.

Blood test revealed pancytopaenia with haemoglobin (Hgb) count of 8.0 g/dl, a white blood cell (WBC) count of 1.1 x 10^9/liter and a platelet count of 16 x 10^9/liter. Blood morphology revealed normochromic normocytic red blood cells (RBCs) with no blasts seen.

Renal profile (RP) showed marginally low sodium level (135 mmol/L) while liver function test (LFT) showed low albumin; 31 g/L. Vitamin B12 level of the patient was 210 pg/ml, which is slightly raised.

Bone marrow aspiration was inconclusive, thus erythropoiesis, leukopoiesis, megakaryopoiesis and granulopoiesis could not be ascertained. Bone marrow trephine showed hypercellular marrow with occasional blasts of cell (<5%) and slightly reduced megakaryocytes which appeared dysplastic. There was no increase in reticulum fibrosis in the trephine. The patient was diagnosed as having MDS-refractory cytopaenia with multilineage dysplasia (RCMD).

Cytogenetics analysis was performed with bone marrow sample obtained by marrow aspiration using a heparinized syringe. Chromosome studies on cells from bone marrow specimen were made by short-term culture (24 hour) in RPMI 1640 culture medium supplemented with 15% fetal bovine serum and penicillin without stimulants. Chromosomes were stained with Leishman staining. Karyotype analyses from G-banded metaphases were performed out according to the International System for Human Cytogenetics Nomenclature (ISCN) 2005. In 13 of 14 metaphases examined, the chromosome 11 has a trisomy configuration as a sole cytogenetic abnormality. The karyotype was 47,XY,+11 as shown in **Fig 1**.

Patient was prescribed with amlodipine 10mg daily, ranitidine 150mg BD, vitamin B, folic acid 5mg and pyridoxine 30mg daily.Subcutaneous administration of Azacytidine; a hypomethylating agent will be part of the treatment plan for this patient. As to date, the patient is alive and is being treated as an outpatient at the Day Care Unit.

DISCUSSION

Here we report a 78-year-old man with MDS-refractory cytopaenia with multilineage dysplasia (RCMD) and a karyotype of 47,XY,+11. It is a rare cytogenetic abnormality in MDS and to the best of our knowledge; this is the first report of MDS with trisomy 11 in Malaysia.

Although many abnormal chromosomal abnormalities have been found to be associated with certain hematologic disorders, there are few reports related to MDS with trisomy 11. In literature, 6 cases (including present case) of MDS and trisomy 11 have been reported to date (**Table 1**) [5-9]. The cases consisted of 1 RA, 1 RCMD, 1 RAEB, 2 RAEB-t and another 1 case was not specified. The age of diagnosis is 12 – 82 years, with female to male ratio of 3 to 4. At the time these cases were reported, three patients were alive (including present case), two had died and another case was not mentioned.

To our knowledge, two of the six reported MDS cases with trisomy 11 had a prior history of malignant disorders, namely, polycythaemia vera (Ohyashiki *et al*., 1989) and aplastic anaemia (Kojima *et al*., 2002). Polycythaemia vera and aplastic anaemia are malignant as they cause late haematological complications of MDS/AML in up to 15% of the cases that are reported (Finazzi *et al*., 2005; Socie *et al*., 1993).

Three of the other cases were de novo MDS and the etiology was unknown for the remaining case. One of the patients with de novo MDS was first diagnosed as having refractory anaemia with excess of blasts in transformation (RAEB-t) with trisomy 11. This progressively transformed to AML M2 within two months and the patient died of pneumonia within a year (Yamamoto *et al*., 1997). Another patient with de novo MDS which was diagnosed as MDS RA died due to severe brain hemorrhage (Tanabe *et al*., 1990). These two cases clearly show that MDS patients with trisomy 11 have a relatively grim clinical outcome. The above observation is further echoed in another study (Wang *et al*., 2010) which suggested that trisomy 11 is best considered as a high-risk cytogenetic abnormality in MDS prognostication due to its clinical aggressiveness towards early/evolving acute myeloid leukemia (AML) with myelodysplasia-related changes.

In the treatment regiment for this patient, subcutaneous administration of Azacytidine was planned. Azacytidine was included as part of the treatment because phosphorylated Azacytidine can bind stoichiometrically to DNA methyltransferases and result in hypomethylation of replicating DNA (Jutterman, Li and Jaenisch, 1994). Studies have shown that p15INK4B; a tumour suppressor gene, is commonly hypermethylated in MDS patients. Therefore, Azacytidine could reverse this effect and induce cell differentiation by demethylating p15INK4B (Christiansen, Andersen and Pedersen-Bjergaard, 2003). This particularly could be beneficial to MDS patients as the immature blasts would be able to differentiate. It is important to note that administration of this substance could result in adverse gastrointestinal and hematologic complications. Nevertheless, these adverse effects are heavily dose dependent and can be controlled by concomitant medications. Moreover, the utilization of Azacytidine to treat MDS patients has been approved by the FDA since 2004 (Kaminskas *et al*., 2005). Therefore, this patient will be treated with Azacytidine. However the dosage administered will be closely monitored so as to minimize the adverse effects associated with this substance.

In conclusion, MDS patients with trisomy 11 should be monitored closely. Although relatively rare, this cytogenetic abnormality cannot be looked upon lightly due to its clinical aggressiveness. It is essential that further research be carried out to investigate the molecular mechanisms that underlie this genetic abnormality. This is turn could lead to the discovery of new drug targets and even cell based therapies which would certainly improve the clinical outcome of MDS patients.

ACKNOWLEDGEMENTS

We would like to thank the staffs of Advanced Diagnostic Lab, AMDI, Universiti Sains Malaysia for their technical assistance.

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Fig 1: G-banded metaphase of bone marrow obtained from the present case showing three copies of chromosome 11 (black arrow).

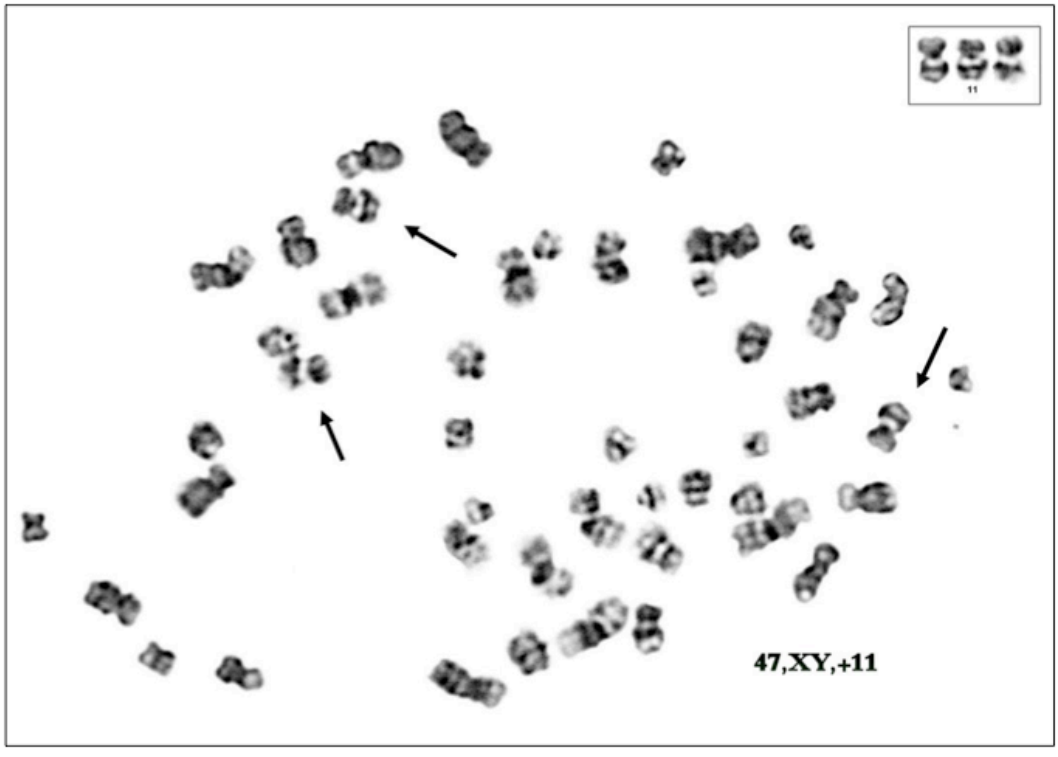

Table I. Reported cases of MDS with +11 as a sole abnormality.

M: Male, F: Female, RAEB-t: Refractory anaemia with excess of blasts in transformation, RA: Refractory anaemia, RAEB: Refractory anaemia with excess of blasts, AML: Acute Myeloid Leukemia, NA: Not Available; RCMD: Refractory cytopaenia with multilineage dysplasia, PB: Peripheral blood, BM: Bone marrow

Year	Country	Age	Sex	Diagnosis	Karyotype	Prior history of malignancy (therapy)	Alive / Died	Reference
1989	Japan	52	M	MDS RAEB-t	PB: 47,XY,+11 (25/30) BM: 47,XX,+11 [3/11]	Polycythemia vera (Chemotherapy)	Alive	7
1990	Japan	59	F	MDS RA	47,XX,+11 (NA)	Not mentioned	Died of brain haemorrhage	8
1997	United States of America	75	M	MDS RAEB-t	47,XY,+11 (NA)	De novo	NA	6
1997	Japan	72	F	MDS RAEB-t Transformed to AML M2	47,XX,+11 (20/20) 47,XX,+11 (8/9) 48,XX,+11,+13 (1/9)	De novo	Died of progressive disease and pneumonia	9
2002	Japan	12	NA	MDS	47,X?,+11 (NA)	Aplastic anaemia (Immunosuppressive therapy)	Alive	5
2011	Malaysia	79	M	MDS RCMD	47,XX,+11 (13/14)	De novo	Alive	Our patient