Two further cases of myelodysplastic syndrome and acute myeloid leukemia with der(5;19)(p10;q10): association with abnormalities involving chromosomes 12 and 21

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Two further cases of myelodysplastic syndrome and acute myeloid leukemia with der(5;19)(p10;q10): association with abnormalities involving chromosomes 12 and 21

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1. Introduction

In the recent issue, we have reported two cases of myelodysplastic syndrome (MDS) with a novel unbalanced whole-arm translocation der(5;19)(p10;q10) [1]. This translocation was accompanied by an additional normal chromosome 19 and described as der(5;19)(p10;q10),+19, which resulted in monosomy 5q and trisomy 19q. Furthermore, both patients presented several common clinical and hematological findings. That is, MDS subtypes were advanced stage, refractory anemia with excess blasts (RAEB)-1 and RAEB-2. Peripheral blood showed leukoerythroblastosis, and marked anemia and thrombocytopenia without neutropenia. Bone marrow demonstrated trilineage dysplasia with prominent dyserythropoiesis. Myeloblasts expressed CD7 as well as myeloid markers. Besides der(5;19),+19, additional cytogenetic aberrations involving chromosomes 6, 17 and 18 were found. These findings suggest that the der(5;19) might constitute a distinct clinical entity in high-risk MDS. In this letter, we report two new cases of MDS and acute myeloid leukemia (AML) arising from MDS with der(5;19).

2. Case reports and results

2.1. Case 1: A 64-year-old man was admitted to our hospital because of anemia in February 2008. Peripheral blood showed hemoglobin 65 g/L, platelets 398 x 10^9/L and white blood cells (WBC) 4.3 x 10^9/L with 9% blasts, 1% myelocytes, 2% metamyelocytes, 4% band forms, 14% segmented neutrophils, 6% monocytes, 4% eosinophils, 1% basophils, and 59% lymphocytes. Two erythroblasts were found among 100 WBC. Bone marrow was hypercellular with 6.2% myeloblasts, 36.8% myeloid cells and 51.8% erythroblasts. Trilineage dysplasia was observed in the bone marrow cells. Especially, dyserythropoiesis including megaloblastic changes and multinucleation of erythroblasts was evident (Fig. 1A). A diagnosis of MDS, RAEB-2, on the World Health Organization (WHO) classification [2], was made. Three months later, he underwent non-myeloablative allogeneic bone marrow transplantation (BMT) from an HLA-matched related male donor. However, he could not obtain complete chimerism and complete remission after BMT. The disease relapsed and finally progressed to AML with myelodysplasia-related changes [2]. He died of disease progression on day 86 after BMT.

2.2. Case 2: A 58-year-old man was referred to our hospital for precise examination of macrocytic anemia lasting for two years and thrombocytopenia. Four years prior, he had received radiotherapy and chemotherapy with cisplatin and 5-fluorouracil for esophageal carcinoma. Peripheral blood showed hemoglobin 67 g/L, platelets 51 x 10^9/L and WBC 6.6 x 10^9/L with 11% blasts, 1% myelocytes, 1% metamyelocytes, 2% band forms, 63% segmented neutrophils, 7% monocytes, 1% basophils, and 14% lymphocytes. Bone marrow was hypercellular with myelofibrosis: 28.2% myeloblasts, 45.0% myeloid cells and 17.2% erythroblasts. Trilineage dysplasia was observed in the bone marrow cells (Fig. 1B). A diagnosis of therapy-related AML, AML arising from previous MDS [2], was made because he had been exposed to cisplatin, as observed in one reported case [1], and had a past history of anemia. Due to severe pneumonia and respiratory failure, he returned to the hospital nearest to his home for best supportive therapies.

Between January 2008 and June 2009, a total of 42 patients with MDS and AML arising from MDS were cytogenetically analyzed in our hospital, and we have found these two cases with der(5;19). Results of cytogenetic analyses during the clinical course are shown in Table 1. In addition to der(5;19),+19, abnormal chromosomes 12 were found by G-banding in both cases (Fig. 1C, 1D). SKY analyses revealed that add(12)(p11.2) in case 1 and dic(12;?)(p11.2;?) in case 2 were derived from complex aberrations consisting of chromosomes 12 and 21: der(12;21) and dic(12;21), respectively (Fig. 2AB). Furthermore, instead of dic(12;21), der(12)t(12;21) was found in a sideline of case 2. A ring chromosome in case 1 originated from a chromosome 6 although breakpoints could not be identified. SKY also confirmed other additional aberrations, t(3;4)(q21;q12) and del(7)(q11.2) in case 1 and der(7)t(7;21) in case 2, as well as der(5;19),+19.

Immunophenotypic analyses showed that blasts in case 1 were positive for CD7, CD13, CD33, CD34 and HLA-DR, as observed in two reported cases (Table 2) [1]. Furthermore, the expression of CD7 considerably increased during the clinical course. On the other hand, blasts in case 2 were positive for CD7, CD13, and CD33, but unexpectedly negative for CD34 and HLA-DR.

3. Discussion

We have identified der(5;19)(p10;q10) in two further cases of MDS and AML arising from MDS. Together with our two previously reported cases [1], four of total 113 cases (3.5%) showed der(5;19) as a single institutional experience. Thus, the der(5;19) was confirmed to be a rare but recurrent cytogenetic aberration in high-risk MDS and AML. It is proposed that der(5;19) could play a crucial role in the pathogenesis of MDS by deletion of 5q and gain of 19q. Interestingly, chromosomes 5 and 19 share common alphoid DNA sequences, D1Z7 and D5Z1, in their centromeric regions [3]. The coexistence of these alphoid subsets in both chromosomes might be conveniently associated with the formation of der(5;19). As expected, the present cases had several clinical and hematological features analogous to those of two reported cases, such as older male, advanced MDS subtype, marked anemia, prominent dyserythropoiesis, and CD7 expression in blasts [1].

As additional cytogenetic aberrations to der(5;19),+19, both cases showed complex abnormalities involving chromosomes 12 and 21, which were not detected in two reported cases [1]. Apparently, all of der(12;21), dic(12;21) and der(12)t(12;21) resulted in total or partial deletions of 12p, whereas deleted regions of chromosomes 21 were variable. Abnormalities of 12p including deletions, unbalanced translocations and dicentrics, most of which lead to loss of 12p materials, have been shown to be found in about 5% of MDS/AML [4]. They are usually associated with prior mutagenic exposure, myelodysplasia, complexly aberrant karyotypes involving chromosomes 5 and/or 7, and a poor prognosis. Among these 12p abnormalities, translocations or dicentrics of 12p with chromosomes 21 seem to be relatively rare events in MDS/AML [4]. Deletions of 7q, one of the most common cytogenetic abnormalities in MDS, were also found in both cases by del(7)(q11.2) and der(7)t(7;21). Del(7q) and del(5q) frequently coexist in MDS with complex karyotypes [5]. Thus, in the present cases, it is suggested that der(5;19) leading to del(5q) and del(12p) as well as del(7q) cooperated in the development of MDS/AML.

A ring chromosome 6 was detected in case 1, supporting our speculation that der(5;19) may be specifically associated with rearrangements of chromosome 6, since these abnormalities rarely occur in MDS [1]. Furthermore, a balanced translocation t(3;4)(q21;q12), which has never been described in the

literature [5], was observed in case 1. Similar to the 3q21q26 syndrome, some chromosome translocations involving 3q21 without 3q26 are associated with dysmegakaryopoiesis and normal or high platelet count in MDS/AML [6]. Thus, the unexpected normal platelet count in case 1 might be due to the presence of t(3;4)(q21;q12).

Surface marker analyses confirmed that the blasts were positive for CD7 in all four cases with der(5;19) [1]. The expression of CD7 in case 1 and one reported case increased during the disease progression, especially at relapse after BMT. These results strongly support the possible specific association of CD7 and MDS with der(5;19). It has been shown that the aggressive clinical behavior in CD7+ MDS patients is due to the cell characteristics of more immature CD7+ myeloblasts including greater proliferative capacity and less apoptosis [7]. These findings may apply to MDS patients with der(5;19) as well.

Recently, in addition to our four cases, only one case of therapy-related AML arising from MDS with der(5;19) has been reported [5, 8], indicating that the usual frequency of der(5;19) is extremely low. The karyotype in one metaphase was 46,XX,der(5;19)(p10;q10),-6,del(7)(q?),add(12)(p11.2),-13,-17,+19. That is, additional cytogenetic abnormalities in this case were similar to those we have reported, although the expression of CD7 was unknown. Interestingly, this case was also reported from Japan [8]. There are some differences in clinical features of MDS including karyotypes between Western and Eastern countries [9]. Thus, ethnic background or environmental influence might be associated with a relatively high prevalence of der(5;19) in Japan. More cases should be studied to clarify whether der(5;19) is particularly associated with CD7 and abnormalities of chromosome 12 and 21.

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Figure legends

Fig. 1.

(A, B) Bone marrow smears of (A) case 1 and (B) case 2 (x1000, May-Grünwald-Giemsa staining). Myeloblasts and trilineage dysplasia, such as megaloblastic changes, multinucleation and karyorrhexis of erythroblasts, hypogranulation and pseudo-Pelger-Huët anomaly of neutrophils, and mononuclear micromegakaryocytes, are shown.

(C, D) Partial G-banded karyotypes of the bone marrow cells. Chromosomes 5, 12, and 19 of (C) case 1 and (D) case 2 are shown. Arrows indicate rearranged chromosomes: (C) der(5;19)(p10;q10) and add(12)(p11.2), and (D) der(5;19)(p10;q10) and dic(12;?)(p11.2;?).

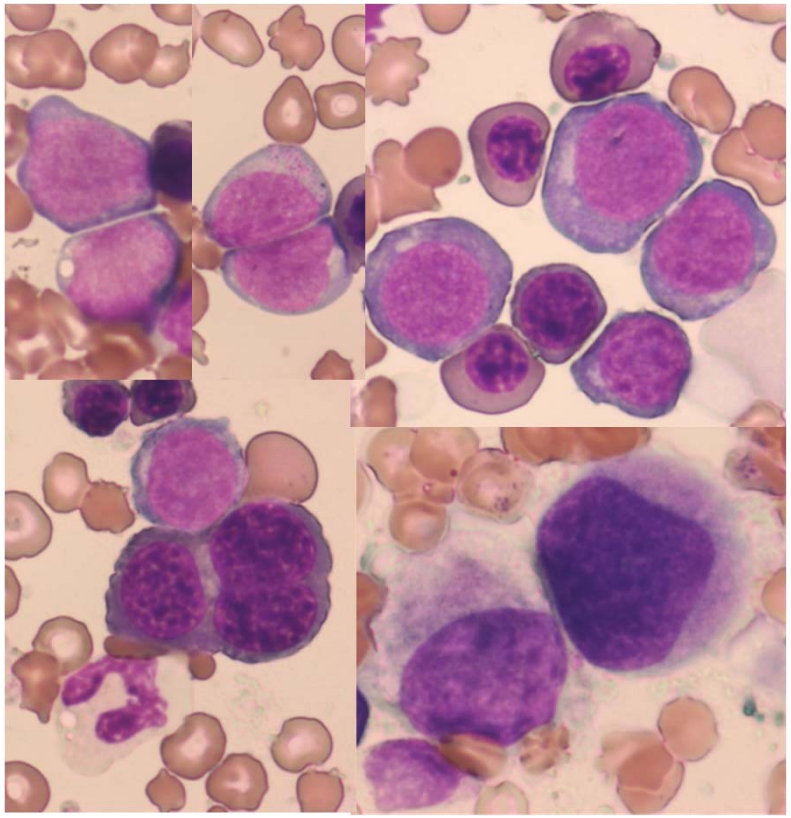
Fig. 2. Spectral karyotyping of the metaphase spreads after spectrum-based classification (left side, reverse DAPI; right side, SKY) of (A) case 1 and (B) case 2. Chromosomes were assigned a pseudocolor according to the measured spectrum. The karyotypes are revised as follows:

(A) 46,XY,t(3;4)(q21;q12),der(5;19)(p10;q10),+r(6),del(7)(q11.2),der(12;21)(q10;q10)del(21)(q?), +19.

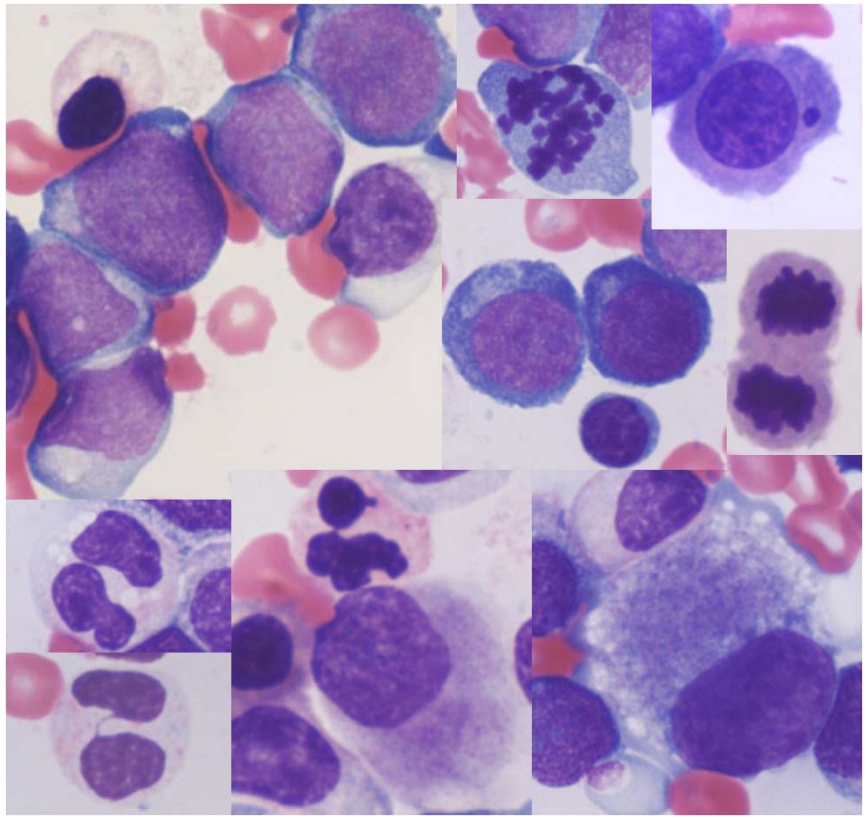
(B) 43,X,-Y,der(5;19)(p10;q10),der(7)t(7;21)(q11.2;q11.2),dic(12;21)(12qter->12p11.2::12?::21p11.2->21q11.2::21q21->21qter),+19,-21. Arrows indicate rearranged chromosomes.

Fig. 1

A



B



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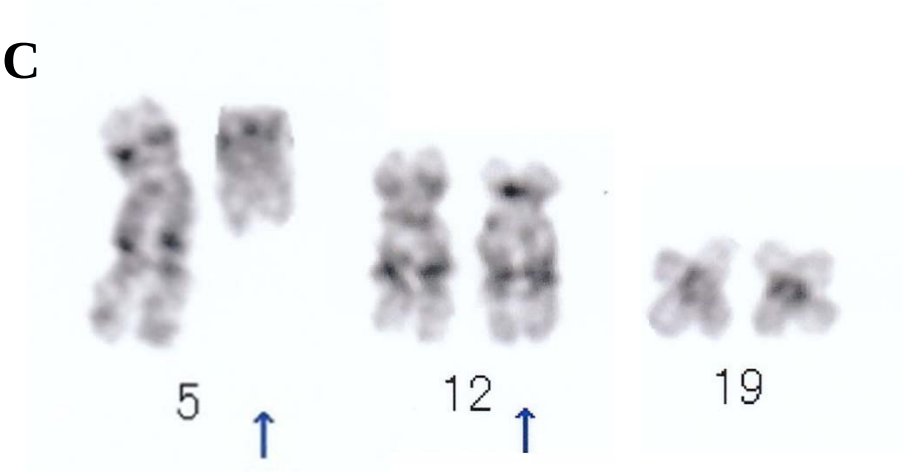

D

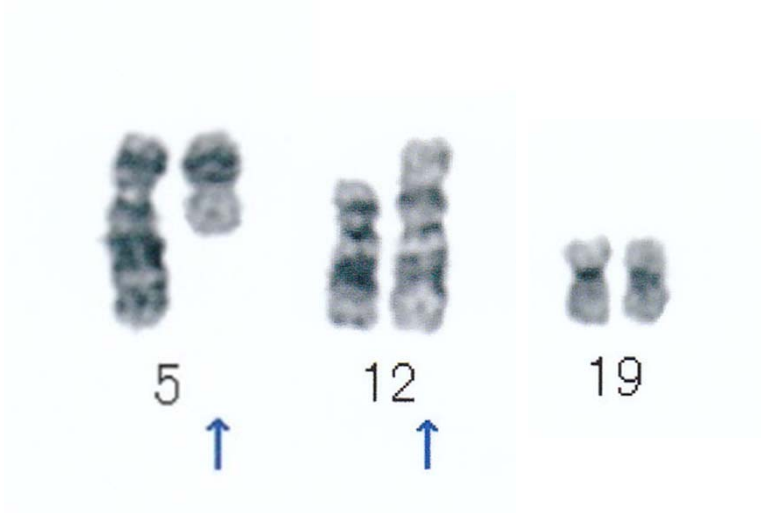

Fig. 2

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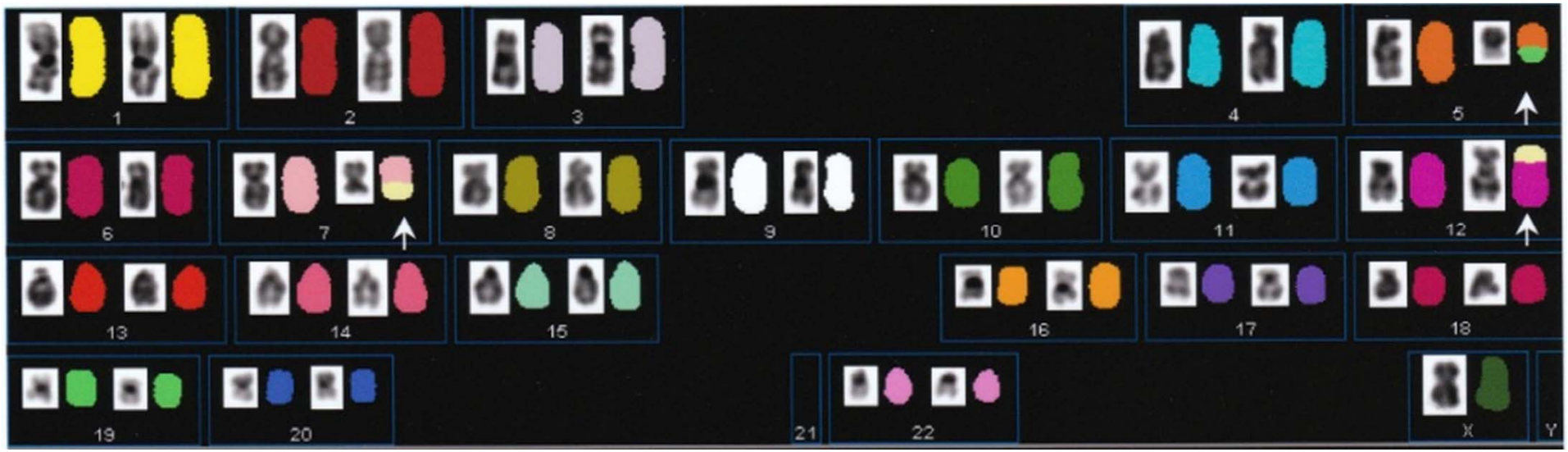
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Table legends

Table 1. Results of G-banding and SKY analyses

Abbreviations: SKY, spectral karyotyping; BMT, bone marrow transplantation.
der(5;19)(p10;q10),+19 is described in bold letters.

Table 2. Results of immunophenotypic analyses

The positive rates of CD antigen expression on the cells surrounded by CD45 low/SSC low gating are shown. *Percentages of gated cells are also shown. Positive data (more than 20%) are described in bold letters.

Table 1. Results of G-banding and SKY analyses

Case	*Date*	*Disease Status*	*Methods*	*Karyotypes by G-banding and SKY*
1	February 2008	diagnosis	G-banding	46,XY,t(3;4)(q21;q12),**der(5;19)(p10;q10)**,del(7)(q11.2),add(12)(p11.2),**+19**,-21,+r1[10]/ 45,sl,add(1)(p36.1),-t(3;4),-22[5]
			SKY	46,XY,t(3;4)(q21;q12),**der(5;19)(p10;q10)**,+r(6),del(7)(q11.2),der(12;21)(q10;q10)del(21)(q?),**+19**[3]/ 45,sl,der(1)(?::22q?::1p36.1->1qter),-t(3;4),-22[2]
	May 2008	progression	G-banding	46,XY,t(3;4)(q21;q12),**der(5;19)(p10;q10)**,+r(6),del(7)(q11.2),der(12;21)(q10;q10)del(21)(q?),**+19**[18]/46,XY[2]
	July 2008	progression, after BMT	G-banding	44-46,XY,t(3;4)(q21;q12),**der(5;19)(p10;q10)**,+r(6),del(7)(q11.2),der(12;21)(q10;q10)del(21)(q?),**+19**[cp11]/ 46,XY[9]
2	August 2008	diagnosis	G-banding	43,X,-Y,**der(5;19)(p10;q10)**,der(7)t(7;21)(q11.2;q11.2), dic(12;?)(p11.2;?),**+19**,-21,-21[7]/44,sl,+add(7)(q11.2), -der(7)t(7;21),add(8)(p21),+add(12)(p11.2),-dic(12;?),-19,+mar1,+mar2[4]
			SKY	43,X,-Y,**der(5;19)(p10;q10)**,der(7)t(7;21)(q11.2;q11.2), dic(12;21)(12qter->12p11.2::12?::21p11.2->21q11.2::21q21->21qter),**+19**,-21[4]/44,X,-Y,**der(5;19)(p10;q10)**, der(7)t(1;7)(?;q11.2),der(8)(2?::8?::19?::8p11.2->8qter),der(12)t(12;21)(p11.2;q21),+der(19)t(8;19)(?;p11), der(21)t(4;21)(?;q22),-21[1]

Table 2. Results of immunophenotypic analyses

Case	*Date*	*CD45 blast gating**	*Positive rate (%)*																
			CD2	*CD3*	*CD4*	*CD5*	*CD7*	*CD8*	*CD10*	*CD13*	*CD14*	*CD16*	*CD19*	*CD20*	*CD33*	*CD34*	*CD41*	*CD56*	*HLA-DR*	*KOR-SA*
1	February 2008	24.9	1.5	0.7	**32.5**	0.6	**24.2**	0.4	3.1	**68.4**	1.3	1.6	1.5	1.0	**74.6**	**66.9**	7.2	1.0	**70.1**	7.3
	May 2008	28.2	2.0	1.3	13.3	1.9	**47.1**	1.5	2.3	**73.4**	3.4	2.8	1.2	1.7	**86.8**	**58.1**	**27.3**	1.6	**79.3**	8.7
	July 2008	78.0	1.6	0.4	**56.5**	0.8	**92.6**	0.4	3.1	**87.2**	1.5	1.2	0.5	1.6	**99.8**	**92.6**	8.6	0.6	**91.4**	2.0
2	August 2008	56.7	0.3	0.4	4.9	0.5	**90.1**	0.4	0.5	**77.7**	0.8	2.3	1.1	0.4	**97.9**	4.0	**61.7**	0.7	10.0	6.6