

# Complex karyotype in myelodysplastic syndromes: Diagnostic procedure and prognostic susceptibility

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## Abstract

Complex karyotype (CK) is a poor prognosis factor in hematological malignancies. Studies have shown that the presence of CK in myelodysplastic syndrome (MDS) can be associated with MDS progression to acute myeloid leukemia. The goal of this review was to examine the relationship between different types of CK with MDS, as well as its possible role in the deterioration and progression of MDS to leukemia. The content used in this paper has been obtained by a PubMed and Google Scholar search of English language papers (1975-2018) using the terms *complex karyotype* and *myelodysplastic syndromes*. A single independent abnormality can be associated with a good prognosis. However, the coexistence of a series of abnormalities can lead to CK, which is associated with the deterioration of MDS and its progression to leukemia. Therefore, CK may be referred to as a prognostic factor in MDS. The detection of independent cytogenetic disorders that altogether can result in CK could be used as a prognostic model for laboratory and clinical use.

## Introduction

Complex karyotype (CK) is a classification of cytogenetic risks of hematologic malignancies associated with a poor prognosis,<sup>1</sup> which has important applications in the diagnosis and prognosis of patients with hematological malignancies, including myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), B-cell lymphoblastic leukemia/lymphoma (B-ALL), chronic myeloid leukemia (CML), chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL), and plasma cell myeloma (PCM).<sup>1-3</sup> There is no clear definition of CK for various types of hematologic malignancies.  $\geq 3$  independent cytogenetic abnormalities in most studies is considered as CK, but in Medical Research Council Acute Myeloid Leukemia 10 trial (MRC AML10),  $\geq 5$  independent cytogenetic abnormalities are deemed as CK.<sup>4</sup> Haase *et al.* demonstrated that the increase in chromosomal abnormalities can be associated with reduced survival rates of MDS patients.<sup>5</sup> In this respect, there are a number of complementary techniques to investigate important chromosomal events involved in the progression of treatment-related secondary myelodysplastic syndrome (t-MDS).<sup>6</sup> For example, spectral karyotyping (SKY), a laboratory technique based on hybridization of 24 fluorescently labeled chromosome painting probes, as well as fluorescence in situ hybridization (FISH), and conventional cytogenetics are techniques used for analysis of CK and t-MDS.<sup>6,7</sup>

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## Complex karyotype as a prognosis predictor in myelodysplastic syndrome

MDS is an abnormality of bone marrow (BM) stem cells associated with monocytopenia, bicytopenias, or pancytopenia.<sup>5,8</sup> Recent studies indicate that up to 30% of de novo MDS cases are associated with CK in initial cytogenetic evaluation.<sup>9</sup> On the other hand, studies have indicated more frequent chromosomal abnormalities in t-MDS than *de novo* MDS. -7 (14%), -5q (28%), -5 (11%), der (21q), +8, -7q, der (12q), t (1;7), -12, der (17q), der (3q), der (3q), and -18 are among the most common chromosomal abnormalities in t-MDS.<sup>10</sup> International Prognostic Scoring System (IPSS) classifies MDS cytogenetic results into four groups of low, int-1, int-2, and high according to the risk of death or transformation to AML. Sconocchia *et al.* state that chromosome 7 anomalies and complex karyotype are placed on a high-risk class.<sup>11</sup> MDS is often transformed to AML, but it can also transform to other leukemia, including acute lymphocytic leukemia (ALL).<sup>12</sup> Each chromosomal abnormality in MDS is shown to be associated with a different prognosis; for example,

del (5q), del (7q)/-5/-7, and +8 are considered to be associated with favorable, unfavorable, and indeterminate prognosis, respectively.<sup>13</sup> On the other hand, has been observed that the higher numbers of the independent cytogenetic abnormalities in MDS patients (usually  $\leq 3$  independent cytogenetic abnormalities), the poorer prognosis of the MDS.<sup>14</sup> As a result, assessment of CK in MDS can be useful in determining prognosis and finding new therapies (Table 1).

## **TP53 mutations and del (5q) with complex karyotype**

### **TP53 mutations**

*TP53* is a tumor suppressor gene (TSGs), the mutation of which can be associated with increased proliferation and survival of tumor cells.<sup>15</sup> In this regard, Wang *et al.* in their recent study have shown that most MDS patients harbor *TP53* mutation and therefore have a poor prognosis.<sup>16</sup> Moreover, del (5q) /-5 > del (7q) /-7 < del (17p) /-17 is observed in MDS patients with CK. No relationship has been found between del (7q) /-7 and del (5q) /-5 with *TP53*;<sup>16-18</sup> on the other hand, since *TP53* gene is located on 17p, coexistence of mutation in 17p region and deletion of chromosome 17 can involve both *TP53* alleles and result in deactivation of both copies of *TP53* gene in a majority of cases. Therefore, simultaneous occurrence of mutation and del (17p), which is associated with a poorer prognosis than the time they occur separately, leads to increased carcinogenesis.<sup>15,19</sup> Also, Cazzola *et al.* demonstrated that coexistence of mutation in chromatin modifiers (*e.g.*, *TET2*, *DNMT3A*, and *ASXL1*) and *TP53* mutation leads to MDS progression and a poorer prognosis (Table 1).<sup>20</sup> Therefore, it may be possible to predict MDS prognosis/progression and transformation to different types of leukemia by examining *TP53* mutations and CK in MDS/progressive MDS to leukemia.

### **Del (5q)**

Del (5q) involves the deletion of q31-q33 on the long arm of chromosome 5<sup>21</sup> that is observed in 10-15% of MDS patients.<sup>22</sup> In this regard, it has been observed that deletion in 5q32-33 region is the most common deletion in del(5q). On the other hand, deletion in 5q31 region is accompanied by a higher risk of MDS and AML.<sup>22</sup> Coexistence of del (5q) and a set of chromosomal abnormalities such as der (1) t(1:2) , -7 , -15, -18, -19 with *TP53* mutation can lead to CK.<sup>23,24</sup> Ammatuna *et al.* demonstrated that MDS with single chromosomal abnormality of del (5q) has a more favorable prognosis in comparison to other chromosomal abnormalities, while del (5q) together with CK will have an unfavorable prognosis.<sup>25</sup> Also, since 5q region harbors genes such as *CSNK1A1*, *RPS14*, *EGR1*, *miR-145* and *miR-146a*, it can be stated that the absence of these genes in del (5q) can lead to selective sensitivity to lenalidomide.<sup>22</sup> On the other hand, it has been observed that CK (including at least two abnormalities in addition to del 5q) in MDS patients is associated with a higher risk of AML progression that can affect the response to lenalidomide. For example, *TP53* mutation can lead to reduced sensitivity to lenalidomide, as well as selective growth of mutant clones.<sup>22,24</sup> Studies have shown that low risk MDS with isolated del (5q) responds well to lenalidomide treatment, but high risk MDS, which is usually associated with CK, has a poor response to lenalidomide treatment.<sup>11,24,26</sup> However, Lionel Ades *et al.* stated that a combination of chemotherapy stimulants like classical

Daunorubicin-AraC with lenalidomide can entail a better response.<sup>27</sup> Therefore, more studies with a higher number of patients are required to assess the effect of drugs such as lenalidomide on the improvement of MDS patients with del (5q) chromosomal abnormality. In this regard, it has been observed that patients with an isolated del (5q) have a better prognosis than those with other chromosomal abnormalities; however, if this chromosomal deletion is accompanied by mutations in *TP53*, there will be a much poorer prognosis.<sup>26</sup> There are a number of genes on 5q chromosome, including *RPS14*, *EGR1*, *NPM1*, *APC*, and *CTNNA1*, each of which is related to *TP53* in some way or other. For example, *NPM1* gene modulates the activity of *TP53* and *CDKN2A* tumor suppressors, and both *EGR1* (a direct transcriptional regulator of tumor suppressor genes like *TP53*, *CDKN1A*, and *PTEN*) and *APC* genes are involved in encoding tumor suppressor proteins (TSP) (Table 1).<sup>27-29</sup> Therefore, further studies on the relationship between *TP53* mutation and del (5q) are warranted.

## **Double minute chromosomes and complex karyotype**

Double-minute chromosomes (DMs) are replicated DNA sequences in tumor cells that contain amplified genes such as *C-MYC*, *MYCN*, *MDM2*, and *EIF5A2*,<sup>30-32</sup> which are typically involved in increased carcinogenesis and poor prognosis of cancer. Bao *et al.* demonstrated that low-dose hydroxyurea (HU) treatment could reduce the frequency of DMs in human cancer cells. On the other hand, ionizing radiation can eliminate amplified genes on DMs;<sup>33</sup> therefore, it can be stated that HU and ionizing agents play a role in the improvement of cancer prognosis. On the other hand, it has been shown that DMs are associated with the frequency of sister chromatid exchange (SCE) in cancer cells and the increased malignancy in cancer.<sup>34</sup> In a study conducted on patients with myeloid malignancies and MDS, it was observed that all patients with *MLL* gene amplification on their DMs were associated with CK like -6, add (8) (q24), der (10) t(10;11), (q28, q13), -11, add (12) (p13), + 13, +13, add (17) (p13), -18, -21, -22, + 1-3 mar, 0~2dmin [Cp20], del (11) (q21q23), add (17) (p13), 20.0 ~ 3dmin [16] / 46, idem, + mar [4].<sup>35</sup> On the other hand, patients with DMs and CK were associated with 17p/*TP53* deletion, so it can be stated that there is a relationship between DMs and CK with a poor prognosis (Table 1).<sup>35</sup> Consequently, conducting further studies on the methods reducing/inhibiting DMs in cancer cells might prevent poor prognosis or MDS progression.

## **Ring chromosome and complex karyotype**

Ring chromosome (RC) is a circular DNA molecule<sup>36</sup> formed by merging of two broken ends of a chromosome, a broken end with the end of telomeres of a chromosome, or the two ends of telomeres of a chromosome.<sup>37</sup> RC is a rare disorder; However, in 75% of AML patients and 97% of MDS patients holder RC mutation, the CK [such as der (9p), der (12) dic (12 ;?19), +15, -18] have been observed.<sup>38,39</sup> Research has shown that RC increase in MDS is associated with progression of MDS to AML. Moreover, MDS patients with CK+RC+ have shorter leukemia-free survival than those with RC+CK-. On the other hand, CK+RC+ AML patients have an overall survival (OS) similar to CK+RC- AML patients, but they have a shorter OS compared to CK-RC+ patients (Table 1).<sup>39,40</sup>

Table 1. Chromosomal abnormalities associated with complex karyotype.

| Cytogenetics  | Mutations  | Clinical findings  | Consequence  | Prognosis                 | Ref.                |
|---|--|--|--|---------------------------|---------------------|
| -5, -7, -17   | Mutation in chromatin modifiers like <i>TEF2-DNMT3A</i> , <i>ASXL1</i>   | <ul style="list-style-type: none"> <li>➤ The simultaneous occurrence of <i>TP53</i> mutations with these mutations and cytogenetics can lead to CK</li> <li>➤ The gene encoding <i>TP53</i> is located on 17p, so the removal of chromosome 17 can cause non-stop cell cycle at G1 stage, inability to induce apoptosis, which ultimately lead to cancer progression due to inability to induce the expression of p21<sup>WAF1/CIP1</sup>, p27<sup>INK1</sup>, and inhibitor of <i>CDK2</i>, 3, 4 and 6.</li> </ul>  | <i>TP53</i> mutations can lead to additive cell growth and also increase cell survival, proliferation, evasion of apoptosis, and chemoresistance                 | Poor                      | 15,19,20,63         |
| -6, add (8) (q24), der (10) t (10;11), (q28, q13), -11, add (12) (p13), +13, +13, add (17) (p13), -18, -21, -22, +1-3 mar, 0 ~ 2dmi [ Cp20], del (11) (q21q23), add (17) (p13), 20,0 ~ 3dmi [16] / 46 | -17p/ <i>TP53</i> mutation and mutation in amplified genes like <i>C-MYC</i> , <i>MYCN</i> , <i>MDM2</i> and <i>E1F5A2</i> | <ul style="list-style-type: none"> <li>➤ The simultaneous occurrence of <i>DMS*</i> with these mutations and cytogenetics can lead to CK.</li> <li>➤ <i>DMS</i> can be treated with low-dose HU and ionizing radiation.</li> <li>➤ <i>MDM2</i> is a <i>MDM2</i> gene protein product identified as an amplified gene on a murine double-minute chromosome.</li> <li>➤ <i>MDM2</i> can act as an ubiquitin-protein ligase to ubiquitinated <i>p53</i> and induce <i>p53</i> nuclear export and its degradation in cytoplasmic proteasomes by binding <i>p53</i> with high affinity.</li> <li>➤ On the other hand, <i>MDMX</i> can act as an upregulator for <i>MDM2</i>.</li> </ul> | <i>MDM2</i> and <i>MDMX*</i> mutations can lead to inhibition of apoptosis, increased cell proliferation, and cancer progression                                 | Poor                      | 30,31,32,34, 35, 64 |
| Der (9p), der(12) dic (12;7;19), +15, -18, -16, del(5) (q13)  | There is still no precise information on mutations that occur predominantly with RC  | <ul style="list-style-type: none"> <li>➤ The simultaneous occurrence of RC with this cytogenetics can lead to CK.</li> <li>➤ <i>RC12</i> contains <i>MDM2</i>, <i>SAS</i>, <i>CDK4</i>, and <i>HMGIC</i> genes that increase proliferation, and expression of these genes can be associated with an increase in carcinogenesis.</li> </ul>   | <i>RC</i> is associated with decreased cell apoptosis and increased proliferation in most types of human neoplasia.  | Poor                      | 38,39,65            |
| Der (1) t(1;2), -7, 15, -18, -19  | Deletion of some genes like <i>RPS14</i> , <i>EGR1</i> , <i>NPM1</i> , <i>APC</i> , <i>CTNNA1</i> and <i>TP53</i> mutation | <ul style="list-style-type: none"> <li>➤ The simultaneous occurrence of the del (5q) with these mutations and cytogenetics can lead to CK.</li> <li>➤ Del (5q) can be treated with lenalidomide.</li> <li>➤ <i>CSNK1A1</i> gene is located on chromosome 5, and studies have shown that heterozygous loss of <i>CSNK1A1</i> is well-tolerated and may lead to the clonal advantage of cells. Nevertheless, homozygous loss of <i>CSNK1A1</i> can lead to cell cycle arrest and apoptosis due to <i>p53</i> activation.</li> </ul>  | MDS with del(5q) is associated with normal to increased megakaryocytes with hypo-lobulated nuclei, erythroid hypoplasia, and normal or increased platelet count  | Poor with AML progression | 22,24,25            |
| -5q, -7q-12, -17, -5t (9;19) (p13; q13), t (6;12) (p21; q13), der (7) t (7;20) (p13;?) t (7;18) (q11; q11), der (18) t(18;22) (q21;q7), der (19) t (7;19) (?:?)                                       | mutation in 11q23  | <ul style="list-style-type: none"> <li>➤ The simultaneous occurrence of der (11) t (11;12) (q23; q13) with these mutations and cytogenetics can lead to CK.</li> <li>➤ Chromosomal translocations involving 11q23 can lead to rearrangements in <i>MLL</i> gene.</li> <li>➤ Therefore, the protein encoded by this gene can be involved in abnormal control of proliferation and differentiation in monocytic progenitor cells and transform hematopoietic cells into leukemia stem cells.</li> </ul>  | der (11) t(11;12) (q23;q13) is associated with pathogenesis of advanced-stage MDS and increased cell proliferation   | Poor                      | 41-45, 66           |
| +11, +22, -20, add (17) (q25), del(5) (q33)   | isochromosome of the long arm of chromosome 17q and 18   | <ul style="list-style-type: none"> <li>➤ Myelofibrosis is mainly associated with these mutations and cytogenetics that contribute to the development of CK.</li> <li>➤ <i>BCL-2</i> gene is localized on 18q21. <i>BCL-2</i> gene product is a protein with anti-apoptotic property.</li> <li>➤ Studies show that isochromosome 18q may mildly increase myeloblasts in peripheral blood through a gene dosage effect.</li> <li>➤ Isochromosome 18q and myelofibrosis are considered as two markers for poor prognosis</li> </ul>   | Isochromosome 18q may be associated with decreased cell apoptosis, increased myeloblasts in blood and eventually, worsening of MDS presenting with myelofibrosis | Poor                      | 47-49               |

Continued on next page.

Table 1. Continued from previous page.

| Cytogenetics  | Mutations  | Clinical findings   | Consequence<br>as two markers for poor prognosis   | Prognosis | Ref.            |
|---|--|---|--|-----------|-----------------|
| T(4;11)(q21;q23), del(5)(q13q33), t(12;13)(p13;q21) [31] / 92, i(17)(q10) [2] / 46,XX [2] | mutation in <i>RAS</i> proteins like Point mutation <i>N-RAS</i> at codon 12 or 13 | <p>➤ The simultaneous occurrence of <i>N-RAS</i> Point mutation with this cytogenetics can lead to CK.</p> <p>➤ <i>RAS</i> proteins are involved in control of cell proliferation, differentiation, and survival through the two pathways of <i>MAPK</i> and <i>PI3K</i>. Studies show that in <i>MAPK</i> pathway, mutations in <i>RAS</i> proteins may result in inability of <i>RAS-GAP</i> protein to activate the inherent Gase enzyme. As a result, due to lack of hydrolysis of <i>GTP</i> molecules, <i>RAS</i> remains active as an alternative for <i>GTP</i> molecules, so this mechanism can cause increasing pro tumorigenic effects by amplifying signaling in the <i>MAPK</i> pathway. On the other hand, in <i>PI3K</i> pathway, it is hypothesized that mutations in <i>RAS</i>, can lead to increased <i>PI3K</i> activity and finally increase cellular growth and evasion of apoptosis through induced mutations in <i>PIK3CA</i> and encoding a truncated version of <i>PI10α</i>.</p> | Point mutation<br><i>N-RAS</i> is associated with disorder in control of cell proliferation, differentiation, survival, and eventual enhancement of cancer progression | Poor      | 53,60-62,67, 68 |

\*MDM2 (MDM2 and MDM4, HDM2, and HDMX in humans), CK: complex Karyotype, Del: deletion, MDS: myelodysplastic syndrome, DMS: double minute chromosomes, RC: ring chromosome, SCE: sister chromatid exchange, T-MDS: therapy-related secondary myelodysplastic syndrome, T7p: short arm of 17 chromosomes, CDK: Cyclin dependent kinases, MDM: mouse double minute, MLL: myeloid/lymphoid leukemia or mixed lineage leukemia, MAPK: mitogen-activated protein kinases, PI3K: phosphoinositide-3 kinase.

## Der (11) t (11;12) (q23; q13) and complex karyotype

Der (11) t (11;12) (q23; q13) is an unbalanced translocation (partial monosomy or trisomy) that occurs non-randomly and may be associated with the pathogenesis of advanced stage MDS.<sup>41,42</sup> Investigations show that der (11) t(11;12)(q23;q13) in refractory anemia with excess of blasts in transformation (RAEB-t), which is a type of MDS, can be associated with a series of chromosomal aberrations such as -12, -17, -5, t(9;19) (p13;q13), t(6;12) (p21;q13),<sup>43</sup> der(7) t(7;20) (p13;?) t(7;18) (q11;q11), der(19) t(7;19), der(18) t(18;22) (q21;q?), deletions of 5q and 7q and lead to CK. CK mainly occurs in advanced stage MDS and is associated with a poor prognosis (Table 1).<sup>41,42,44,45</sup> Therefore, by conducting further studies on the relationship between der (11) t(11;12) (q23;q13) and advanced stage MDS, der (11) t (11;12) (q23;q13) might prove a target for advanced stage MDS therapeutic methods.

## Myelofibrosis and complex karyotype

Myelofibrosis is a rare disorder associated with BM fibrosis and accumulation of immature precursors of three hematopoietic cell lines.<sup>46-47</sup> It can be associated with MDS and a number of chromosomal abnormalities such as -18, -20, +22, +11, add (17)(q25), del(5)(q33), and isochromosome of long arm of chromosome 18.<sup>47-49</sup> Elizabeth E et al. indicated that if MDS is accompanied with fibrosis and chromosomal abnormalities, the prognosis will be poorer than the case MDS is associated with chromosomal abnormalities without fibrosis (Table 1).<sup>50</sup> Therefore, BM biopsy together with cytogenetic study is suggested in MDS patients presenting with a decrease in hematopoietic cell lineages and splenomegaly.

## N-RAS point mutation and complex karyotype

*RAS* isoforms, which include *N*-, *K*-, and *H-RAS*, are GTPases that play a role in cell growth, differentiation, migration, and apoptosis.<sup>51,52</sup> Therefore, mutations in *RAS* isoforms are dominant mutations in MDS and AML subtypes such as acute megakaryoblastic leukemia (AML-M7).<sup>53</sup> Studies have shown that a point mutation in the gene encoding *N-RAS* at codon 12 is one of the most common mutations in MDS and AML-M7, which could possibly contribute to the progression of MDS to AML-M7.<sup>54,55</sup> A number of studies have suggested a mechanism for MDS development *via* uncontrolled proliferation of hematopoietic cells independent of growth factors, which is followed by mutations in *RAS* proto-oncogene and its signaling pathway.<sup>56-58</sup> Nevertheless, other studies indicate that compared to other mutations in *RAS* isoforms, aspartate substitution with glycine in *N-RAS* codon 12 is capable of maintaining  $\geq 40\%$  activity of wild type GTPases, which can be considered as another mechanism for mutation in the cell.<sup>55,59</sup> As a result, no exact mechanism has been described for the relationship between mutation of *RAS* isoforms and MDS progression to AML. In this regard, during the progression of MDS to AML, *N-RAS* point mutation can occur together with chromosomal anomalies such as t (4;11) (q21;q23), del(5) (q13q33), t (12;13) (p13;q21) [31] / 92, XXXX, idem  $\times$  2 [6] / 46, XX, i (17) (q10) [2] / 46, XX [2] to result in CK;<sup>60-62</sup> therefore, these chromosomal abnormalities can be associated with a poor prognosis. Teresa de Souza Fernandez *et al.* indicated that isochromosome 17q and polyploidy were probably caused by genetic instability due to transformation

of MDS into malignant leukemia (Table 1).<sup>62-65</sup>

Figures 1 and 2 show several examples of independent chromosome aberrations in CK.

## Discussion and Conclusions

CK, which refers to independent chromosomal abnormalities ( $\geq 3$  independent chromosomal abnormalities), is among the worst risk factors of MDS patients. An increase in the number of chromosomal abnormalities in MDS has been related with poorer

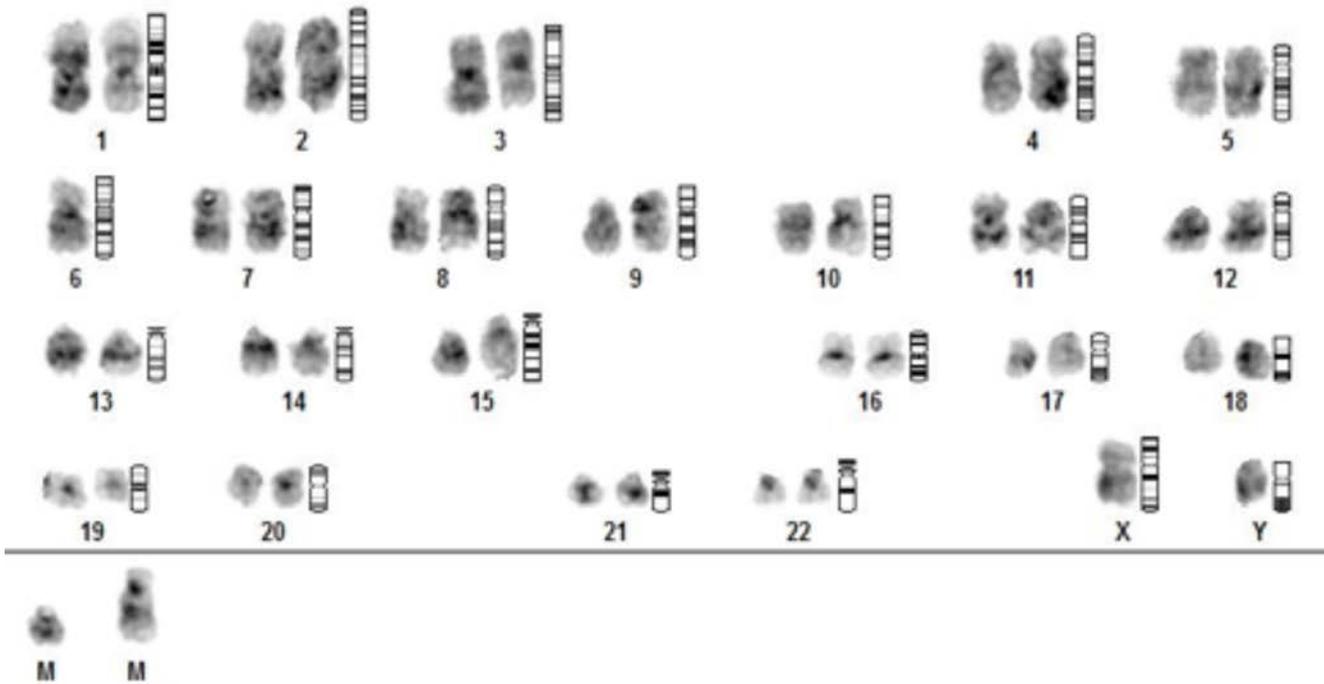


Figure 1. Examples of CK, including independent chromosome aberrations such as -6, der (9) (12), +2mar.

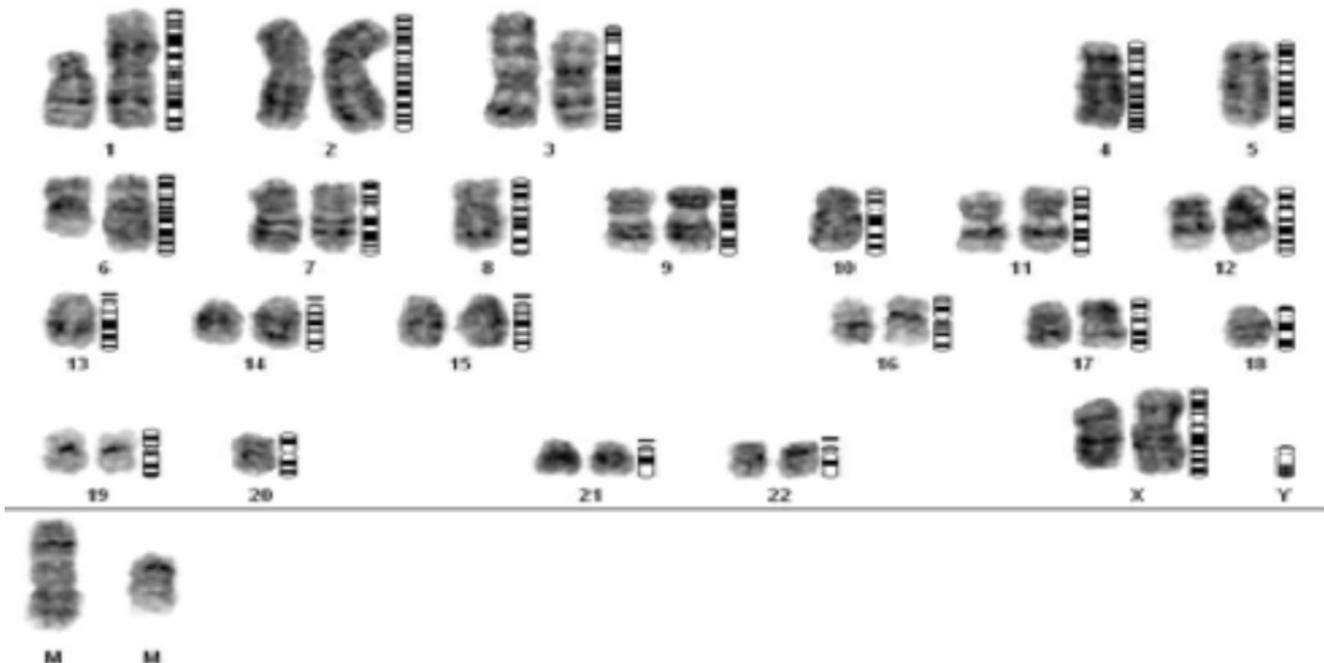


Figure 2. Examples of CK, involving independent chromosome aberrations such as -4, -5, -8, -10, -13, -18, -20, der (1)(6), +2mar.

prognosis, decreased OS, and increased progression to AML, although the prognosis of an isolated chromosomal abnormality can be different with its prognosis in CK. For example, del (5q) by itself is associated with a good prognosis and lower progression rates to AML, while when associated with other genetic abnormalities to form CK, del (5q) has a poorer prognosis and higher AML progression rates. On the other hand, patients with CK having at least four independent chromosomal abnormalities show an increased risk of relapse. CK can also affect a number of drugs applied to treat MDS or leukemia, reducing the effectiveness of the drug in treatment of the disease. However, according to studies, it may be argued that the degree of CK interference with effectiveness of drug can be different based on the types of independent chromosomal abnormalities that form CK. Therefore, by conducting studies focusing on a series of chromosomal abnormalities involved in the formation of CK, approaches can be introduced to determine the prognosis of MDS and prevent the progression of MDS to leukemia and its relapse.

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