Chapter

Chromosome Abnormalities in Hematological Malignancies and Its Clinical Significance

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Abstract

The latest version of the World Health Organization guidelines focuses mainly on the genetic and cytogenetic features of hematologic neoplasms as predictors of diagnostic, treatment decision, prognostic outcome, and for treatment monitoring in hematological malignancies. There are different techniques to identify these abnormalities. Live cells are needed for chromosome preparation. The Hematological malignancies include myeloid and lymphoid neoplasms. The myeloid neoplasms include Myelodysplastic syndromes, myeloproliferative neoplasms, and acute myeloid leukemias. The Lymphoid neoplasms include acute and chronic lymphocytic leukemias, plasma cell neoplasms, myeloma, hodgkin, and non-hodgkin lymphomas. The first chromosomal abnormality discovered in connection with cancer is the Philadelphia chromosome, which is an abnormal chromosome 22, formed due to the translocation between chromosomes 9 and 22. The presence of this abnormal chromosome confirms the diagnosis of "CML". After that, hundreds of chromosomal abnormalities have been identified in hematological malignancies in different parts of the world. In AML, specific abnormalities were identified as having a good prognosis, intermediate prognosis, and poor prognosis. In other hematological malignancies also there some specific chromosome abnormalities are associated with prognostication. Now a day's clinicians depend mainly on genetic abnormalities for the proper treatment management of hematological malignancies, so the study of chromosomal abnormalities is essential.

Keywords: hematological malignancies, chromosomes, abnormalities, cytogenetics, karyotype, leukemia, lymphoma

1. Introduction

In hematological malignancies, the study of chromosomal abnormalities is essential for the proper diagnosis, prognosis prediction, treatment decision, and treatment monitoring. The important technique used for the study of chromosomal abnormalities are the conventional cytogenetics, the advanced techniques like Fluorescent In situ Hybridization (FISH), Spectral Karyotyping (SKY)/ Multiplex Karyotyping/MFISH, and, to some extent, array comparative genomic hybridization (array CGH), have enhanced the knowledge of chromosome abnormalities in hematologic neoplasms [1]. The cytogenetic study requires the presence of live cells or at least intact nuclei. Human cancer cells divide spontaneously and without culturing, chromosomes could be prepared from the sample [2]. These

techniques have contributed immensely to the discovery of significant cryptic rearrangements in various tissue preparations of leukemia and other cancers. The advanced techniques in cytogenetics FISH, SKY, and CGH are seen as a potential competitor to conventional cytogenetics, due to their higher resolution. Still conventional cytogenetic analysis remains as the best method for the diagnosis of most hematologic neoplasms since it has the advantage of an overall examination of all chromosomes at a glance. Conventional cytogenetics help to identify distinct clonal populations, which are not possible by FISH and practically impossible by array CGH [3, 4].

2. Myeloid neoplasms

Myelodysplastic syndromes (MDS), Myeloproliferative neoplasms (MPN), MDS/MPN, and acute myeloid leukemias are included in this group. The classification of myeloid neoplasms has recently been modified considering the genetic and cytogenetic abnormalities [5].

2.1 Myelodysplastic syndromes (MDS)

MDS is a heterogeneous group of hematopoietic neoplasms with an increased risk of transformation into acute myeloid leukemia (AML) via a multistep process [6]. Chromosomal studies are essential for both diagnostic and prognostic information. In about 50% of patients chromosome abnormalities could be observed. The severity of the disease is associated with the frequency of chromosomal abnormalities [7, 8]. About 25% of patients with low-grade MDS, such as refractory anemia and refractory anemia with ring sideroblasts, have an abnormal karyotype, compared with 50–70% of patients with refractory anemia with excess blasts (RAEB-1 and RAEB-2). The karyotypes observed in MDS are variable as they present with single or complex chromosome rearrangements [9, 10]. The most frequent chromosome abnormalities are complete or partial loss of chromosomes 5 and/or 7, deletions on the long arm of chromosome 20, and gain of chromosome 8 [11]. In general, aggressive neoplasms are characterized by more complex karyotypes than those seen in low-grade MDS. Furthermore, as a general rule, dosage aberrations appear to be more represented in primary MDS, whereas balanced translocations are encountered more frequently in secondary MDS. Complex karyotypes with loss/deletion of chromosomes 5 and/or 7 together with deletions of 6p, 12p, and/or 16q are typical in therapy-related MDS, whereas balanced translocations involving 11q23 and 21q22.3 are associated with preceding therapy with DNA topoisomerase II inhibitors [12]. According to the presence of chromosome abnormalities, MDS is classified into different risk groups. 12p-, 9q-, t(15q), 15q-, +21, 5q-, 20q-, -X, -Y, t(19), t(7q), -21 and normal Karyotype are considered as good prognosis. Patients with abnormalities +8,11q-, +18 are included in the Intermediate I group. The presence of abnormalities like t(11q23), any 3q abnormality, +19, 7q-, complex abnormalities (less than 3 abnormalities) are included in the Intermediate II group. Complex abnormalities (more than 3 abnormalities), 3q21.3q26.2, t(5q), 7q/monosomy 7 are considered as poor prognosis [13]. The significance of trisomy 15 with or without the loss of the Y chromosome is not fully understood. Apparently balanced translocations have been reported in MDS, involved with chromosomes 1, 2, 3, 5, 6, 7, 13, 15, 17, 18, 19, and 20 appear to be more frequent, but they appear to be less common than the unbalanced rearrangements [14].

2.2 Myeloproliferative neoplasms (MPNs)

Myeloproliferative neoplasms are hematopoietic stem cell disorders characterized by the proliferation of one or more myeloid cellular elements in the marrow and mostly affect adult individuals. Chronic myelogenous leukemia (CML), polycythemia vera (PV), primary myelofibrosis (PMF), essential thrombocythemia (ET), chronic eosinophilic leukemia (CEL), systemic mastocytosis, chronic neutrophilic leukemia (CNL), and the unclassifiable MPNs [5].

2.3 Chronic myelogenous leukemia

Chronic myelogenous leukemia (CML) is a hematopoietic stem cell disease, most frequently seen in adults. It is characterized by a biphasic or triphasic clinical course in which a benign chronic phase is followed by transformation into an accelerated and blastic phase [15, 16]. The hallmark of CML is the presence of the "Philadelphia chromosome" (Ph), which is the first chromosome abnormality identified to have been associated with a specific malignant neoplasm. The Ph chromosome was first described in 1960 by Nowell and Hungerford and is named after the city in which it was discovered [17]. Because of a reciprocal translocation between chromosome 9 and 22; a major portion from the q arm of chromosome 22 is translocated to the q arm of chromosome 9 and a small portion from the q arm of 9 is translocate the q arm of 22, leads to a shortened chromosome 22, called the Philadelphia chromosome. The t (9;22) (q34;q11.2), leads to the formation of a chimeric transcript between the *ABL1* and *BCR* genes at 9q34 and 22q11.2, respectively [18]. This BCR-ABL fusion gene formed in chromosome 22 is responsible for CML. The main abnormality seen in the chronic phase of CML is t(9;22). Variant translocation due to the involvement of one or more additional chromosomes is observed in about 6% of cases, whereas in approximately 3% of cases the translocation cannot be identified by routine cytogenetics [19]. These variants and cryptic rearrangements generally have the same prognostic outcome of the standard t(9;22), but some are associated with a more aggressive course. Conventional cytogenetic analysis can sometimes reveal abnormalities in addition to the t(9;22). It is important to note, however, that an additional balanced rearrangement in all metaphase cells in chronic phase CML might be constitutional in origin. Additional abnormalities are associated with the accelerated phase or blast crisis, and are characterized by an increase in the number of blasts and worsening of clinical symptoms [20]. The most recurrent chromosome abnormalities (about 90% of cases) in these phases are an additional Ph chromosome, +8, i(17) (q10), and/or +19. Other abnormalities, such as −Y, −7, +21, +19,del(7q), 11q23 del, t(8;21)(q22;q22.3), t(15;17) (q24.1;q21.2), inv. (16)(p13.1q22.1), as well as 3q21.3, 3q26.2, 3 way Ph, 4 way Ph and 11q23 rearrangements have been reported but only in a small number of cases [21].

2.4 Polycythemia vera (PV)

PV is most commonly seen in men over the age of 50, but anyone can develop PV. These patients typically experience an increased number of white blood cells, an increased platelet count, and an enlarged spleen, especially over time, which in some patients leads to bleeding and thrombosis [22]. About 14–20% of patients with PV have karyotypic abnormalities at the time of initial diagnosis. However, the cytogenetic abnormalities in PV have not been well characterized and their prognosis impact is largely unknown. At the chromosome level, patients are *BCR-ABL* fusion-negative, other abnormalities detected are +1, +8, +9/+9p, and/or del (20q). Furthermore, a gain of 9p is usually the result of a derivative chromosome, the most

common of which is a der (9; 18) (p10; q10). This gain is often the result of unbalanced translocations. When the disease progresses abnormalities like del (5q), del (7q), and/or del (17p) appear [23–25].

2.5 Primary myelofibrosis (PM)

Primary myelofibrosis, also known as idiopathic myelofibrosis and agnogenic myeloid metaplasia, is characterized by an increased number of megakaryocytes and immature granulocytes and associated anemia. Affected patients are generally in their 5th and 6th decade of life [26]. Chromosome abnormalities are observed in about 40–50% of cases at diagnosis. del(13q), del(20q), and gain of chromosome 8 are the commonly seen abnormalities, and additional abnormalities such as del (5q), del (7q), gain of 1q, and del (17p) are detected during disease progression [27].

2.6 Essential thrombocythemia (ET)

ET is most commonly seen in women over the age of 50, characterized by an increased number of platelets in the peripheral blood. Chromosome abnormalities could be seen in about 10% of cases. The commonly seen abnormalities are +8, +9, del(13q), and del(20q), less commonly gain of 1q, del(5q), and del(7q). As in other MPNs, karyotypic abnormalities are more frequent during disease progression to MDS or AML [28].

2.7 Systemic mastocytosis (SM)

Systemic mastocytosis, often termed systemic mast cell disease (SMCD), is characterized by infiltration of clonally derived mast cells in different tissues, including bone marrow, skin, the gastrointestinal (GI) tract, the liver, and the spleen [29]. Most Patients with systemic mastocytosis (SM) are characterized by symptoms such as hepatomegaly, osteoporosis, and ascites. This is a very complex disease, as it comprises several distinct entities and is also found in association with neoplasms such as MPN and leukemia [29]. Chromosome abnormalities reported are +8, +9, del(7q), del(11q), del(20q), t(8;21), inv.(16)/t(16;16) and rearrangements involving chromosome 4 [30].

2.8 Chronic neutrophilic leukemia (CNL)

CNL is a rare *BCR-ABL* negative myeloproliferative neoplasm (MPN) characterized by sustained, predominantly mature neutrophil proliferation, bone marrow granulocytic hyperplasia, and hepatosplenomegaly. As the name implies, it is characterized by an increase in the number of mature neutrophils [31]. Approximately 20% of cases have an abnormal karyotype. The abnormalities observed so far include +8, +9, del(11q), del(20q), +21, and less frequently del(12p) [32].

2.9 Chronic myelomonocytic leukemia (CMML)

CMML happens when monocytes in the bone marrow begin to grow out of control and is characterized by persistent monocytosis and a variable degree of dysplasia [33]. Although no specific abnormality has been associated with CMML, recurrent chromosome abnormalities, such as –7/del(7q), a gain of chromosome 8, and less commonly del(5q), 12p rearrangements, i(17)(q10) and t(5;12)(q33.1;p13.2) have been observed [34].

2.10 Juvenile myelomonocytic leukemia (JMML)

JMML is a rare MPN that predominantly affects young children under the age of four, characterized by an abnormal proliferation of myelocytes and monocytes in the bone marrow [35]. The most common abnormality is −7/del (7q) and less frequently del(5q). The final diagnosis is based on the exclusion of the translocation 9:22 [36, 37].

2.11 Acute myeloid leukemia (AML)

AML is characterized by an increase in the number of myeloid cells in the marrow and an arrest in their maturation, frequently resulting in hematopoietic insufficiency, with or without leukocytosis. At least 20% of blasts should be present in the marrow. The classification AML has been revised by the WHO by considering the various genetic and cytogenetic changes. Although AML more frequently affects adults in their 5th decade of life, it has been described in children and young adults also [38]. AML is associated with characteristic recurrent, acquired chromosomal abnormalities, and many are reciprocal translocations that generate a fusion gene, others involve partial or complete loss or gain of a chromosome. Cytogenetic findings are important for the diagnosis and classification of AML and some are associated with distinctive clinicopathologic features, have prognostic significance, and /or influence in the choice of therapy [39]. Recurrent Genetic Abnormalities seen in AML are t(8;21)(q22;q22.3), inv.(16) (p13.1q22.1) or (16;16)(p13.1;q22.1), t(15;17)(q24.1;q21.2), t(9;11)(p22;q23), t(6;9)(p23;q34.1), inv.(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2), and t(1;22)(p13.3;q13.1). As per WHO classification, AML is classified into good, intermediate, and poor prognostic categories according to the presence of specific chromosomal abnormalities [40]. The abnormalities associated with favorable outcome in AML are t(8;21)(q22;q22.3), inv.(16)(p13.1q22.1) or t(16;16)(p13.1;q22.1), t(15;17) (q24.1;q21.2) Intermediate prognosis group include t(9;11)(p21.3;q23.3), adverse group are t(6;9)(p23.1;q34.1), t(v; 11q23.3), t(9;22)(q34.1;q11.2), inv.(3)q21.3;) or t(3;3), −5 or del(5q), −7, −17, abn(17p), complex karyotype and monosomy karyotype. The presence of additional abnormalities in patients with good prognostic features changes the overall disease prognosis. The most frequent additional abnormality in patients with t(8;21) is loss of a sex chromosome (the Y in males), followed by del(9q), del(7q), +8, and/or +21. Other additional chromosome abnormalities seen in patients with inv.(16) include +8, del(7q), and/or + 21and +22 [41, 42]. Acute Promyelocytic Leukemia (APML), is a subtype of AML with the recurrent abnormality t(15;17) (q24.1;q21.2). Originally considered one of the most aggressive leukemias, it is now a model for targeted therapy. Additional abnormalities frequently been observed in *APL*, are +8, del(9q), and del(7q) [43]. In about 5-10 % AML patients, MLL rearrangements at 11q23 could be seen. Among the identified 85 known *MLL* translocations, the majority are of with poor outcomes. Other frequent *MLL* translocation are t(11;19), t(6;11)(q27;q23), t(10;11)(q21.3;q23), inv.(3)(q21.3q26.2) or t(3;3) (q 21.3;q 26.2). The most common additional abnormalities that are seen in cases with rearrangements of 3q21.3 and 3q26.2 are −7 and, less frequently, del(5q) [44, 45].

2.12 Acute megakaryoblastic leukemia (AMKL)

AMKL is a clonal stem cell neoplasm that comprises between 4%and 15% of newly diagnosed pediatric AML patients [46]. This is commonly regarded as a subtype of AML, with the median age at presentation between 1 and 8 years. AMKL is extremely rare in adults, occurring in only 1% of AML cases. In pediatrics this

disease is divided into two major subgroups: AMKL patients with Down Syndrome (DSAMKL) and AMKL patients without DS (non-DS AMKL). The incidence of developing DS- AMKL is 500 fold higher than in the general population [46]. The main abnormality seen is t (1; 22) which is diagnostic in this group and is considered as with intermediate prognosis. Chromosome abnormalities at diagnosis are observed in about 50% of adult patients and the most common rearrangements seen are in regions 3q21.3 and 3q26.2. Other abnormalities seen frequently are −5/del(5q), −7/del(7q), and +8 [46].

2.13 Myeloid sarcoma (MS)

Myeloid sarcoma or granulocytic sarcoma is a rare disease that can present as an extramedullary leukemic tumor, concurrently with or at relapse of AML. This is also known as chloroma, although in some rare cases it may present in non-leukemic patients also [47]. MS may be common in patients included in FAB class M2, WHO classification (2016) in a separate entity under 'AML and related neoplasms' and those with cytogenetic abnormalities t(8;21) or inv.(16). The common cytogenetic abnormalities observed in myeloid sarcoma are −7, +8, del(5q), del(20q), +4, +11, del(12p), del(16q), del(13q), del(9p), del(9q), del(6q), del(15q), del(4q), inv.(16)/t(16;16), MLL rearrangements, and t(8;21)(q22;q22.3). The prognosis is variable as it is influenced by several factors including but not limited to age, morphology, and cytogenetic abnormality [48–50].

3. Lymphoid neoplasms

Lymphoid neoplasms are derived from cells that normally develop into T Lymphocytes or B Lymphocytes (lymphocytes or plasma cells). This includes Acute and chronic lymphocytic leukemias, plasma cell neoplasms, myeloma, Hodgkin and Non-Hodgkin lymphomas. This group of hematologic neoplasms includes immature and mature neoplasms of B-cell, T-cell, and natural killer (NK) cell subtypes [51, 52]. This leukemia is more common in children than in adults. The majority of lymphoid neoplasms (both precursor and mature types) are characterized by recurrent chromosome abnormalities [53].

3.1 Acute lymphoid neoplasms

This neoplasm is defined as leukemia when it involves the bone marrow and peripheral blood and as lymphoma when it presents as a lesion without evidence of bone marrow and peripheral blood involvement. Approximately 85% of B-ALL patients are children [53–55]. Chromosome abnormalities are useful for prognostic stratification in acute neoplasms. Abnormalities like t(9;22)(q34;q11.2), 11q23 (MLL) rearrangements, t(1;19)(q23.3;p13.3), and hypodiploidy (≤45 chromosomes) in children are known to have an unfavorable prognosis, whereas t(12;21)(p13.2;q22.3) and hyperdiploidy (>50 chromosomes) are associated with a favorable prognostic outcome. t(9;22) (q34;q11.2) appears in approximately 2.5% of children and approximately 25% of adults with B-ALL [56, 57] . Chromosome abnormalities in addition to the t(9;22) are seen in more than 60% of patients, specifically +8 and one extra copy of the Ph chromosome. Other abnormalities seen in B-ALL are −7, +X, and del(9p). MLL translocations are also found BLL which include t(4;11) (q21.3;q23), t(11;19) (q23;p13.3), t(6;11)(q27;q230 and t(9;11)(p22;q23) [58–61]. MLL rearrangements are associated with an unfavorable prognostic outcome in both children and adults. t(1;19)(q23.3;p13.3) is another abnormality that is seen in approximately 5%

of children with pre-B-ALL. About 75% of patients show an unbalanced and 25% show a balanced form of this translocation, the unbalanced form in pediatric B-ALL patients is associated with a better prognostic outcome than the balanced form [62]. Three separate groups of hypodiploidy have been observed and are associated with an unfavorable prognosis. The most common is the near-haploid karyotype, with a chromosome count ranging from 26 to 29. The second is with chromosome count ranging from 30 to 39 and the third group with 40 to 44 chromosomes. Generally, a lower number of chromosomes correspond to a worse prognosis. Hyperdiploidy with chromosomes 51 and 55 is found to be associated with a relatively less favorable prognosis than those from 56 to 68 chromosomes. The presence of trisomies 4 and 10 are seemed to be with a better prognosis. The most common gains involve chromosomes 4, 6, 8, 10, 14, 17, 18, 19, and 21. The prognostic outcome of adult B-ALL patients with hyperdiploidy is not as favorable as in children. High hyperdiploidy is associated with poor prognosis [63–65]. Another abnormality often seen in children between 2 and 12 years old is the translocation t(12;21)(p13.2;q22.3) and is associated with a long duration of first remission and excellent cure rates. Another abnormality, del(9p) appears to be associated with improved outcomes in adults poor outcomes in children with B-ALL. Abnormalities like, dic(9;20)(p13.2;q11.2), dic(9;12) (p13.2;p12.2), and i(9)(q10), are associated with an excellent prognostic outcome. The most common rearrangements involving 14q32.3 observed in B-ALL are, t(8;14) (q11.2;q32.3), inv.(14)(q11.2q32.3), t(14;14)(q11.2;q32.3), t(14;19) (q32.3;q13.1), and t(14;20)(q32.3;q13.1) [64, 66, 67]. Approximately 10% of adults and 2% of children with B-ALL these translocations are more frequent. A rare translocation t(5;14)(q31.1;q32.3), has also been observed in B-ALL and is usually associated with eosinophilia. Other reported translocations are t(6;14)(p22.3;q32.3) and t(9;14)(p13.2;q32.3). Two cryptic translocations, t(X;14)(p22.3;q32.3) and t(Y;14) (p11.3;q32.3) have recently been described in B-ALL, especially in patients with Down syndrome. The abnormalities were usually seen in T-ALL involve 14q11.2, 7q35, 7p14. A rare but recurrent abnormality seen in T-ALL is inv. (14) (q11.2q32.1) or t(14;14) (q11.2;q32.1) [68–74].

3.2 Non-Hodgkin lymphoma (NHL)

NHL is a type of cancer that begins in the lymphatic system, comprises a heterogeneous group of disorders characterized by localized proliferation of lymphocytes. In non-Hodgkin's lymphoma, lymphocytes grow abnormally and can form tumors throughout the body. The most reliable criteria for the classification of malignant lymphomas are genetic abnormalities. The most common chromosome anomalies associated with specific lymphomas include t(14;18) (q32.3;q21.3) in follicular lymphoma (FL), t(8;14) (q24.2;q32.3) in Burkitt lymphoma (BL), t(11;14) (q13;q32.3) in mantle cell lymphoma (MCL), and t(11;18)(q21;q21.3) in mucosa-associated lymphoid tissue (MALT) lymphoma [75, 76].

3.3 Follicular lymphoma (FL)

FL is typically a slow-growing or indolent form of non-Hodgkin lymphoma (NHL) that arises from B-lymphocytes, making it a B-cell lymphoma. This lymphoma subtype accounts for 20–30% of all NHL cases. About 85–90% of patients with FL and 25–30% of patients with diffuse large B-cell lymphoma (DLBCL) exhibit (14;18)(q32.3;q21.3). Variant translocations, such as t(2;18)(p12;q21.3) and t(18;22)(q21.3;q11.2) have been described in both FL and DLBCL. Additional abnormalities in addition to t(14;18), certain numerical abnormalities, specifically trisomies 2, 7, and/or 8, are associated with a more favorable outcome.

Whereas patients with structural abnormalities, specifically del(1p), del(1q), del(6q), +der(18), or del(22q), or gain of an X chromosome or chromosome12, which are associated with an unfavorable outcome. Secondary abnormalities including +7, del(10q), del(6q), and/or +der(18) leads to the progression of FL to DLBCL occurs in 60–80% of cases [77–80].

3.4 Burkitt lymphoma (BL)

BL is a rare but highly aggressive B-cell NHL. This disease may affect the jaw, central nervous system, bowel, kidneys, ovaries, or other organs. Burkitt lymphoma may spread to the central nervous system (CNS). The most common abnormalities seen are t(8;14)(q24.2;q32.3), which is seen in about 75–80% of patients, t(8;22)(q24.2;q11.2) and t(2;8)(p12;q24.2), which are seen in 10% and 5% of patients, respectively [81, 82].

3.5 Diffuse large B-cell lymphoma (DLBCL)

DLBCL is the most common type of NHL, accounting for about 22% of newly diagnosed cases of B-cell NHL in the United States. In 25–30% of cases t(14;18)(q32.3;q21.3) is observed. Additional abnormalities seen are rearrangements of 1q and 3q, del(6q), +7, +8, del(10q), del(11q), +12, del(13q), rearrangements of 14q and 17p, +der(18)t(14;18), and +X. The more complex the karyotype the worse the prognostic outcome. Translocations involving 3q27 are found in approximately 35% of patients. More than 30 different partner genes have been translocated with this locus, the most recurrent of which include 2p12, 3q29, 4p13, 6p21.2, 6p22, 7p12, 8q24.2, 11q23, 13q14, 14q32.3, 15q22, 16p13, 17q11.2, 18p11.2, and 22q11.2. Other recurrent abnormalities observed are partial or complete gain of chromosome 3, specifically 3q; loss of chromosome 6; and gain of chromosome 18 and t(14;15)(q32.2;q11.2). Among these abnormalities, the only gain of chromosome 3 is associated with an adverse prognosis [83–88].

3.6 Mantle cell lymphoma (MCL)

MCL is typically an aggressive, rare form of NHL, in which about 95% of patients exhibit t(11;14)(q13;q32.3). t(2;11)(p12;q13), t(11;22) (q13;q11.2)], have been observed in a limited number of cases, but their detection is equally important for the diagnosis of MCL. t(12;14)(p13;q32;3), t(6;14)(p21;q32.3), t(2;14)(p24;q32.3), partial or complete gain of chromosomes 3 and 8, gain of 15q, and losses of 1p, 8p, 9p, 11q, 13q, loss of 9p, 17p, and gain of 3q and 8q, have also been described in MCL [89–92].

3.7 Mucosa-associated lymphoid tissue (MALT) lymphoma

This is a slow-growing type of non-Hodgkin lymphoma and, it most commonly develops in the stomach (when it is called gastric MALT lymphoma) but it can develop in other parts of the body also (which is called non-gastric MALT lymphoma). t(11;18)(q21.3;q21.3) is one of the specific chromosome aberrations occurring in 50% of MALT lymphoma cases. When present, this translocation is usually the only chromosome abnormality. The other specific translocation is (14;18)(q32.3;q21.3), which is observed in about 2% of cases. Abnormalities like, t(1;14)(p22.3;q32.3) and its variant t(1;2) (p22.3;p12 and t(3;14)(p13;q32.2) are also been observed [93–95].

3.8 Lymphoplasmacytic lymphoma (LPL)

This disorder presents with symptoms related to bone marrow infiltration and IgM monoclonal gammopathy. In approximately 50% of LPL cases, the deletion of 6q is observed, followed by a gain of chromosome 4 in 20% of cases, and abnormalities such as del(17p) and gains of chromosomes 3 and 7 in the small number of cases. The prognostic significance of chromosome abnormalities is unclear [96].

3.9 Splenic marginal zone B-cell lymphoma [SMZL]

SMZL represents a rare chronic B lymphocyte proliferative disease, which only accounts for about 1–2% of non-Hodgkin's lymphoma. Recurrent numerical and structural abnormalities are observed in SMZL. Deletion of 7q is one of the most common structural abnormalities, which is seen in approximately 30–40% of cases. In 30–50% of cases partial or complete trisomy 3 is seen and in 20–30% of cases partial or complete trisomy, 12 is observed. Deletion of 17p is seen in some aggressive cases in addition to these abnormalities [97–100].

3.10 Chronic lymphocytic leukemia (CLL)

CLL is an indolent B-cell neoplasm that leads to the proliferation of mature, normal-appearing lymphocytes in the peripheral blood, bone marrow, spleen, and lymph nodes. This is a type of non-Hodgkin lymphoma. The most important risk factor for the development of CLL is a positive family history. The prognosis is highly dependent on the presence of recurrent chromosome abnormalities, specifically del(6)(q23.3), del(13q)(q14.3), +12, del(11)(q22.1), and del(17)(p13.1) [101]. The presence of del(13q) is a sole abnormality and is considered as having a good prognosis. The deleted portion of chromosome 13 can vary in size, but it always involves band 13q14.3. Trisomy 12 is considered the second most common abnormality in CLL. Additional abnormality del (13q) is seen along with the gain of chromosome 12 in most cases and less frequently, del(11q) and del(17p), believed to occur mostly as clonal evolution. The presence of +12 together with del(14q) or t(14;18) has also been reported [102–105]. Deletion of 17p is another abnormality associated with loss of *TP53* at 17p13.1, are characterized by a poor response to chemotherapy and short survival. The majority of abnormalities leading to del(17p) are unbalanced translocations. Generally, the loss of 17p is present in the context of a complex karyotype. However, a few cases with i(17)(q10) as the only change have been described. Deletion of 6q is rarely the sole abnormality and this abnormality is considered an intermediate marker in CLL. Translocations involved chromosome 14 observed in CLL include t(11;14)(q13.q32.3), t(2;14)(p16.1;q32.3), t(14;19)(q32.3;q13), and t(14;18)(q32.3;q21.3), and their variants [105–110]. Rarely, t(8;14)(q24.2;q11.2) is observed as an additional abnormality in some CLL cases. Another recurrent translocation found to involve chromosome 13 is t(6;13)(p21;q14.1) or t(10;13)(q24;q14) [111, 112].

3.11 B-cell prolymphocytic leukemia

B-cell prolymphocytic leukemia (B-PLL) is a rare chronic lymphoproliferative neoplasm comprised of prolymphocytes, typically with involvement of the peripheral blood, bone marrow, and spleen, accounting for only 1% of all chronic leukemias of lymphoid origin. The important abnormalities reported are t(11;14), gain

of chromosome 12, and deletions of 6q, 11q, 13q, and 17p, abnormalities. Additional abnormalities seen in some cases of PLL are the t(8;14), t(2;8), and t(8;22). In approximately 50% of cases, rearrangements of chromosome 17 leading to loss of 17p13.1 have been reported [113, 114].

3.12 Hairy cell leukemia (HCL)

HCL is a rare slow-growing B-cell lymphoproliferative neoplasm that accounts for 2% of all B-cell lymphomas. This affects more men than women, and it occurs most commonly in middle-aged or older adults. There are no specific chromosome abnormalities in HCL. However, a recurrent gain of chromosome 5, specifically the region 5q13-q31, and deletion of chromosome 7, specifically the region 7q22-q36 are demonstrated by conventional cytogenetics. Abnormalities involve chromosomes 1, 6, 14, and 19 are less frequently observed [115, 116].

3.13 Multiple myeloma (MM)

Multiple myeloma accounts for approximately 12% of hematologic neoplasms. This affects the terminally differentiated plasma cells in the bone marrow and presents with an excess of plasma cells in the bone marrow [117]. Chromosome abnormalities have been crucial in the characterization of prognostically significant markers in MM. Hypodiploidy (<46 chromosomes) with loss of chromosome 13, or chromosome 17, are associated with an unfavorable prognosis. In the majority of cases, the hypodiploid chromosome complement includes structural abnormalities, involving, in particular, chromosomes 1, 4, 6, 14, 16, and 20. Specifically, loss of 1p and/or gain of 1q, losses of 4q and 6q, loss and/or rearrangements of 14q and 16q, and partial or complete loss of chromosome 20 are most commonly seen. Translocations involving chromosome 14, are seen in approximately 85% of the cases, which include translocations, t(4;14)(p16.3;q32.3), t(14;16)(q32.3;q23.1), and t(14;20) (q32.3;q12) which are associated with an unfavorable prognosis. Karyotypes with 70–90 chromosomes and a double content of structural rearrangements, including the relative losses of chromosomes 13 and 17, most likely represent the doubling of a hypodiploid clone. Another group of MM patients is characterized by hyperdiploidy and few or no structural abnormalities. Gains are nonrandom and often involve chromosomes 3, 5, 7, 9, 11, 15, 19, and 21. Patients with the presence of these additional chromosomes are placed in a standard-risk category, as long as there is no deletion of 13q or 17p. The most common translocation in MM is t(11:14)(q13;q32.3) and is present in approximately 25% of cases and is associated with improved prognostic outcomes. The prognostic relevance of hyperdiploid karyotypes might be difficult to ascertain when structural abnormalities are present. An interstitial deletion of 13q, involving either 13q14.2 or 13q14.3, is one of the most common abnormalities in MM and has been detected in over 50% of cases. When other abnormalities present along with del(13q) appears to be with a poor prognosis. The prognostic outcome of a hyperdiploid karyotype typically associated with standard-risk myeloma is not altered by the presence of del(13q). On the other hand, in a hypodiploid karyotype, del(13q) or loss of chromosome 13 shows a poor prognosis. In approximately 10% of MM patients deletion of 17p has been observed which leads to deletion of 17p13.1 (*TP53*) and is believed that it occurs as secondary events during disease progression. This deletion is seen in both hypodiploid and hyperdiploid karyotypes. Contrary to what is seen with deletion of 13q, deletion of *TP53* has a negative impact, irrespective of the presence of favorable prognostic markers. Abnormalities involving chromosome 1 in MM include deletions of 1p, gains of 1q, and/or translocations involving either arm.

Deletions of 1p most frequently involve the segment between bands 1p12 and 1p31, whereas gain of 1q involves the segment q21 → qter or the entire long arm. Gain of 1q is the second most frequent chromosomal abnormality seen after del(13q). Among the translocations involving chromosome 1, the majority are derivatives of rearrangements involving various chromosomes, resulting in a gain of 1q. The common recurrent unbalanced translocations leading to gain of 1q are der(1;15)(q10;q10), der(1;16)(q10;p10), and der(1;19)(q10;p10). The most frequent non-random chromosomal partners found in translocations with 14q32.3, are t(11;14)(q13;q32.3), t(4;14)(p16.3;q32.3), and t(14;16)(q32.3;q23.1). t(11;14), is detected in about 20–25%, t(4;14)(p16.3;q32.3) is detected in approximately 15% and t(14;16)(q32.3;q23.1) is observed in approximately 5–7% of MM patients. Similarly to t(4;14), tends to occur in hypodiploid karyotypes, together with deletions of 13q and/or 17p, and this abnormality is placed in a high-risk prognostic category. Two other translocations, t(6;14)(p21.1;q32.3) and t(14;20)(q32.3;q12), have also been described in MM [118–126].

3.14 Hodgkin lymphoma (HL)

HL comprises approximately 30% of all lymphoma cases. HL affects individuals of all age groups with two preferential peaks, one occurring between the ages of 15 and 30 years and the other at 60 years. The majority of HL patients show a normal karyotype, abnormal chromosome complement is found in a minority of cases. There are no specific chromosome abnormalities been detected in HL. The common finding is that the karyotypes tend to be hyperdiploid, with 60–70 chromosomes. There are some recurrent abnormalities which include losses of 1p, 6q, 7q, 13q, 16q, and 17p; gains of 2p, 9p, and chromosome 12, as well as rearrangements of 3q27 [127, 128].

3.15 T-cell prolymphocytic leukemia (T-PLL)

T-PLL is a rare aggressive malignancy with poor response to conventional treatment and short survival. This affects approximately 2% of adults aged 30 years and over. The most common sites of involvement include peripheral blood, bone marrow, lymph node, and other hematopoietic organs such as the spleen and liver. T-PLL is with distinctive clinical, morphologic, and cytogenetic features. The most common chromosome abnormalities are inv.(14)(q11.2q32.1), t(14;14)(q11.2;q32.1), and t(7;14)(q34;q32.1). The most common translocation in this group is t(X;14)(q28;q11.2). In the majority of cases, additional abnormalities are observed, which include i(8)(q10) or other rearrangements leading to gain of 8q, deletion or rearrangements of 11q, and deletions of 6q, 12p, and 17p [129–131].

3.16 Adult T-cell leukemia/lymphoma (ATLL)

ATLL is a rare and often aggressive T cell Lymphoma that can be found in the blood (Leukemia), lymph nodes (Lymphoma), skin, or multiple areas of the body. Very complex karyotypes are observed in ATLL patients. The most frequent abnormalities include rearrangements of 7p14.1, 7q34, and 14q11.2; gains of the X chromosomes and chromosomes 3 and 7; rearrangements of 1p, 1q, 2q, 3q, and 17q; and deletions of 6q, 9p, 13q, and 17p. The prognosis associated with these abnormalities is considered an unfavorable prognosis. Abnormalities of 1p, 1q, 3q, and 14q and deletions of 2q, 9p, 14q, and 17p are found to be associated with poor prognosis [132–135].

3.17 Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS)

PTCL, NOS is a broad category of biologically and clinically heterogeneous diseases that cannot be further classified into any other of the existing entities defined by the WHO classification. Highly complex Karyotypes are usually seen with rearrangements that often lead to losses of 6q, 9p, 10q,13q and gains of 3q, 7q, and 8q and the prognosis is considered as poor for most patients. The t(5;9)(q33.3;q22.2) is an important translocation seen in these lymphomas [136, 137].

3.18 Angioimmunoblastic T-cell lymphoma (AITL)

AITL is a rare aggressive form of Non-Hodgkin's lymphoma which is a group of related malignancies. This accounts for approximately 2% of all non-Hodgkin's lymphomas but represents the most common subtype (15–20%) of peripheral T-cell lymphomas. Complex Karyotypes are seen and often show a gain of 11q13 and gains of chromosomes 3, 5, and an X chromosome, as well as losses of 5q, 10q, and 12q. Gain of 11q13 may represent a primary event in angioimmunoblastic T-cell lymphoma [138].

3.19 Anaplastic large cell lymphoma (ALCL)

ALCL is a rare type of NHL and is one of the subtypes of T cell Lymphoma ALCL comprises about 1% of all NHLs and approximately 16% of all T cell lymphomas [127]. The cytogenetic hallmark is the presence of specific translocations involving the anaplastic lymphoma kinase gene (ALK) and various partner chromosomes. The most common *ALK* translocation is t(2;5)(p23.1;q35.1), which fuses part of the nucleophosmin gene (*NPM1*) located at 5q35.1 with *ALK* located at 2p23.1, leading to activation of *ALK* [139, 140].

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