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RESEARCH ARTICLE

A CASE OF MYELODYSPLASTIC SYNDROME WITH RARE TRANSLOCATION (2-11) (Q31; P15) SECONDARY TO CHEMOTHERAPY TREATMENT

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Abstract

Chromosomal translocations are common genetic alterations in myeloid neoplasia, and certain translocations have been specifically associated with secondary myeloid neoplasms following treatment with Topoisomerase II inhibitors. The most frequently observed translocations involve chromosomes 11q23 (MLL) and 21q22 (Runx1), and they typically occur early after chemotherapy. Here, we present a rare case of secondary myelodysplastic syndrome that occurred 14 years after chemotherapy, which included both alkylating agents and Topoisomerase II inhibitors. The patient presented with a translocation t (2;11) (q31; p15), which resulted in a rearrangement of the Nup98 gene with the HOXD13 gene. To our knowledge, this is the first reported case of this specific translocation in the literature. This case underscores the importance of continued vigilance for the development of secondary myeloid neoplasms in patients who have received chemotherapy and suggests the need for further research to better understand the genetic mechanisms underlying these rare translocations.

Introduction:-

Myelodysplastic syndrome (MDS) secondary to treatment with chemotherapy and/or radiotherapy is a well-known complication of hematologic malignancies and solid tumors. The World Health Organization (WHO) 2016 classification of myeloid neoplasms and acute leukemia categorized this entity as Treatment-Related Myeloid Neoplasms (t-MN) [1]. The most recent update to the WHO classification in 2022 further categorizes t-MN as a form of secondary myeloid neoplasia, which encompasses both those arising from cytotoxic treatment and those arising from germline predisposition [2]. T-MN is further subdivided into MDS, acute myeloid leukemia (AML), and MDS/MPN overlap syndromes, collectively referred to as t-MDS, t-AML, and t-MPN/MDS [2]. Although t-MN accounts for 15-20% of all MDS cases [3], its incidence is increasing with the use of chemotherapy and radiotherapy protocols that offer prolonged or slow overall survival [4].

The pathogenesis of treatment-related myeloid neoplasia (t-MN) is thought to arise through several mechanisms, including direct induction of a fusion oncogene, induction of genetic instability, selection of a pre-existing hematopoietic cell clone, and inherited susceptibility to cancer [5].

The clinical presentation of treatment-related myeloid neoplasia (t-MN) is similar to that of de novo MDS, and therefore, a thorough questioning of the patient's medical history should be conducted, particularly about previous

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exposure to chemotherapy and/or radiotherapy. Family history should also be evaluated to assess for possible genetic predisposition to cancer [6].

Cytogenetic abnormalities are a hallmark of treatment-related myeloid neoplasia (t-MN), with a 90-95% frequency in affected cases. The most common chromosomal aberrations observed in t-MN include complex karyotypes, monosomy of chromosomes 5q and 7q, deletion of chromosomes 5q and 7q, translocation of chromosome 11q23, translocation of chromosome 21q22, t(15;17) translocation, inversion of chromosome 16, and t(17;19)(q22;12) translocation [7].

The translocation t (2;11) (q31; p15) leading to a rearrangement of the NUP98 gene is a rare anomaly that has been reported in myeloid neoplasia secondary to treatment [8].

Molecular abnormalities frequently found in treatment-related myeloid neoplasia include mutations in TP53, Spliceosome genes, and ASXL1 [7].

The prognosis for patients with t-MN is generally poor and is impacted by unfavorable cytogenetic and molecular abnormalities, comorbidities, previous treatments, and initial pathology [9].

In this report, we present a case of a patient with myelodysplastic syndrome following cytotoxic treatment who was found to have a rare translocation (2;11) (q31; p15).

Observation:-

A male patient, aged 48 years, with a history of stage III Aa Hodgkin's lymphoma in 2008, was treated with four cycles of ABVD (Adriamycin-bleomycin-vinblastine-dacarbazine) without response. He subsequently received six cycles of ICE (Ifosfamide-carboplatin-etoposide) with a partial response, which was consolidated by an autologous peripheral stem cell transplant using a BEAM (Bicnu-etoposide-Aracytin-mephalan) conditioning regimen on July 31, 2009. This resulted in complete metabolic remission.

In October 2021, the patient presented with symptomatic IgG Kappa multiple myeloma involving the kidney and complicated by Randall's syndrome. The International Staging System (ISS) score was 3, and FISH analysis revealed normal findings, with no detectable 17p deletion or 4-14 translocation.

The patient received 6 cycles of VCD (Velcade-Cyclophosphamide-Dexamethasone) and achieved an 84% partial response. Subsequently, he underwent peripheral stem cell autotransplantation after intensification with Mephalan at a dose of 140mg/m2 on July 22, 2022.

The individual's evolution was characterized by the manifestation of an aregenerative bicytopenia in November 2022, which was comprised of an aregenerative normocytic normochromic anemia and thrombocytopenia. The complete blood count (CBC) revealed the following results: hemoglobin (Hb) 9 g/dl, mean corpuscular volume (MCV) 89 fl, mean corpuscular hemoglobin concentration (MCHC) 33g/dl, mean corpuscular hemoglobin (TCMH) 29 pg, reticulocyte count 36000/mm3, white blood cell count (WBC) 3200/mm3, neutrophil count 2240/mm3, monocyte count 260/mm3, lymphocyte count 540/mm3, and platelet count 45000/mm3.

The blood smear did not reveal any abnormalities, and the results of the hemostasis workup were within the normal range (prothrombin time [PT] 79%, activated partial thromboplastin time [APTT] 1.1, and fibrinogen 3.8 g/l).

The etiological evaluation of peripheral cytopenia, including vitamin levels, thyroid function, inflammation markers, and viral serologies, returned negative results. A myelogram was performed, revealing a rich marrow where all cell lineages were present with multilineage dysplasia but without an excess of blasts (only 4% of blasts present). Furthermore, there was a hyperplasia of the erythroid lineage at 66%, but without the presence of sideroblasts in the crown (images 1 and 2).

Bone marrow biopsy (BOM) showed a morphological appearance and an immunohistochemical profile indicating hyperplastic bone marrow without tumor infiltration.

The bone marrow cytogenetic analysis identified the presence of a translocation t (2-11) (q31; p15):46, XY, t (2-11) (q31; p15) [1]/46, XY [39], as well as a rearrangement of the NUP98 and HOXD13 genes detected via fluorescence in situ hybridization (FISH).

This case of myelodysplastic syndrome is classified as high-risk, with a Revised International Prognostic Scoring System (R-IPSS) score of 4.4. Notably, it occurred 14 years after the individual's first chemotherapy treatment for Hodgkin's lymphoma, which involved the use of alkylating agents and ITI II.

The possibility of an allogeneic stem cell transplantation was considered as a curative treatment for this patient. However, due to the individual's chronic renal failure (glomerular filtration rate [GFR] of 32 ml/min) and massive proteinuria, which were not responsive to myeloma treatment, the risk of transplant-related mortality (MRT) was deemed too high, and this procedure was not pursued.

Instead, the individual was started on erythropoiesis-stimulating agents (ESA) and a thrombopoietin (TPO) agonist if the thrombocytopenia was deep and symptomatic. This treatment approach was chosen as an alternative to transplantation.

Discussion:-

Cytogenetic abnormalities specific to myeloid neoplasia secondary to treatment are classified into two subgroups correlated to the causative treatment. In approximately 70% of cases (2/3), these abnormalities are represented by monosomy of 5q, deletion of 5q, monosomy of 7, deletion of 7q, and/or deletion or monosomy of chromosome 17. These abnormalities typically occur 5 to 7 years after exposure to alkylating agents and/or radiotherapy. The clinical presentation is that of a myelodysplastic syndrome, which often rapidly progresses to acute myeloid leukemia (AML) and has a poor prognosis [10].

In 30% of cases, the cytogenetic abnormalities specific to myeloid neoplasia secondary to treatment involve a translocation between the KMT2A gene (11q23.3) and the RUNX1 gene (21q22.1), which typically occurs 2 to 3 years after exposure to topoisomerase II inhibitors. The clinical presentation in such cases is acute myeloblastic leukemia, and eligible patients have an excellent response to intensive therapy [10].

The t(2;11) translocation (q31;p15), which generates a rearrangement of the NUP98 gene and a HOXD13-NUP98 fusion transcript, has been described in neoplasia secondary to therapy, including therapy-related acute myeloid leukemia (t-AML) [8].

NUP98 is an important component of the nuclear pore complex, a multi-protein structure that is integrated into the nuclear membrane and facilitates the bidirectional transport of ions, polypeptides, and macromolecules, including proteins and mRNAs, between the nucleus and cytoplasm [11]. NUP98 is predominantly located in the nucleus and plays a crucial role in the transcriptional regulation of genes involved in cell differentiation and cell cycle regulation.

However, fusion genes involving NUP98 have been implicated in the generation of genomic instability, leading to the development of malignant clonal evolution. These fusion genes occur when the NUP98 gene becomes fused with another gene, resulting in a chimeric gene that drives aberrant cellular behavior, including uncontrolled proliferation, apoptosis inhibition, and cell cycle dysregulation [12]. The HOXD13-NUP98 fusion transcript generated by the t (2;11) translocation has been shown to promote leukemogenesis by disrupting the normal function of both the HOXD13 and NUP98 genes [13].

The NUP98 gene has been found to fuse with several partner genes, both HOX and non-HOX genes, and experimental mouse models have shown that such fusions can lead to the development of hematological malignancies such as myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) [12]. HOX genes are transcription factors that are essential in embryonic development but can also contribute to oncogenesis by promoting cell proliferation, resistance to apoptosis, and tumor progression [13].

Numerous instances of Nup98 rearrangements with Hox genes have been documented in the scientific literature. The first such instance was the translocation t (7;11) (q15; p15.5) in 1996, which overlapped with the NUP98-HOXA9 gene and was implicated in de novo AML and MDS as well as t-AML/t-MDS [14-15]. Subsequent discoveries included the t (2;11) (q31; p15) translocation, which fused the NUP98-HOXD13 genes [8], and the t

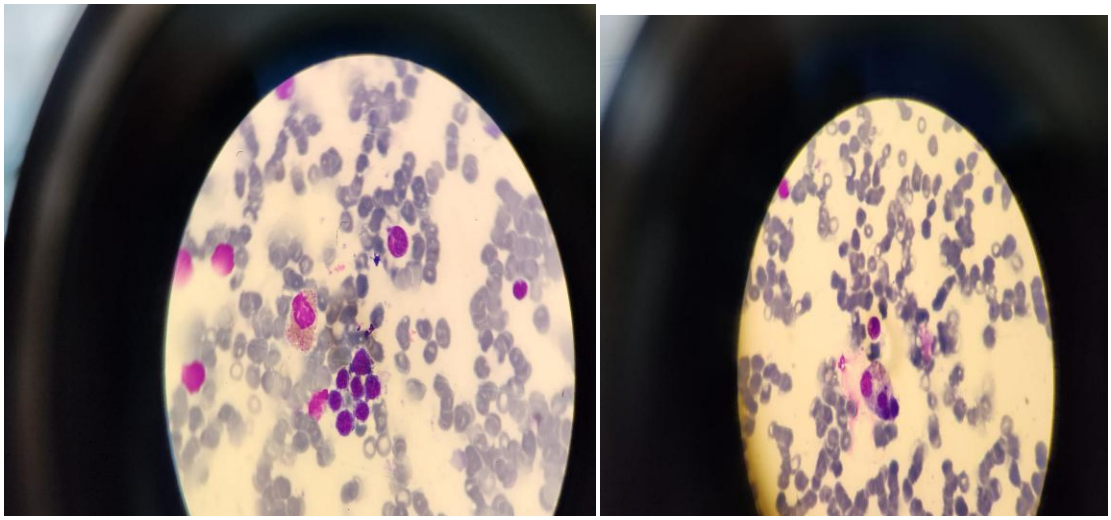
(1;11) (q23; p15) translocation, which generated a NUP98-PMX1 fusion transcript [16]. These rearrangements were associated with t-AML and t-AML/t-MDS, respectively.

In cohorts of 410 and 574 patients with de novo adult and pediatric AML, respectively, the frequency of NUP98 rearrangement is estimated to be approximately 3.7% to 3.8% [17,18]. However, NUP98 rearrangement is more commonly observed in myeloid neoplasia resulting from prior treatment [8,19].

Studies involving case cohorts of patients with hemopathy and Nup98 rearrangement have consistently reported an unfavorable prognosis, which is often characterized by the recurrence of FLT3-ITD, WT1, and epigenetic molecular mutations [17-20]. Peripheral stem cell allograft has been identified as the sole curative option for these patients, with some evidence suggesting that it can improve prognosis [17-20].

To the best of our knowledge, this is the first reported case in the scientific literature of NUP98-HOXD13(t 2-11) rearrangement (q31; p15) in a patient with myelodysplastic syndrome resulting from prior treatment.

In summary, translocation (2-11) (q31; p15) is a rare occurrence in myelodysplastic syndromes that develop secondary to cytotoxic treatments. Patients with this translocation have a poor prognosis, with a high likelihood of progressing to AML.



Images 1, 2:-

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