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ACUTE MYELOID LEUKEMIA AND NON-SEMINOMATOUS GERM CELL TUMOR IN A PATIENT WITH KLINEFELTER SYNDROME

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INTRODUCTION

Klinefelter Syndrome (KS) is an inherited genetic disorder characterized by the presence of an extra X chromosome, affecting males and usually diagnosed in adulthood. It has been reported to be associated with extragonadal germ cell tumors (GCTs) and hematologic malignancies (histiocytosis, myelodysplastic neoplasia, and AML M7), which are often refractory to treatment. A common clonal origin has been suggested based on the presence of i(12p) and trisomy 8.

CASE

-We present the case of a 20-year-old male with a history of Klinefelter syndrome.
-He presented with symptoms of cough, dyspnea, and anterior chest pain, with infra-scapular hypoventilation on examination. Contrast-enhanced chest CT revealed an anterior mediastinal tumor with vascular compression. Elevated AFP and B-HCG levels led to a diagnosis of GCTs. He received three cycles of BEP regimen (Bleomycin, etoposide, and cisplatin) with disease progression.
- Persistent pancytopenia prompted a hematologic evaluation, revealing AML with 20% blasts, with an immunophenotyped compatible with acute myeloid Leukemia
-He was not a candidate for intensive treatment and initiated a regimen with azacytidine and Venetoclax due to a functional status of KPS 70%.
-The patient decides not to accept further treatment and dies

DIAGNOSIS STUDIES

Flow cytometry : CD34+, MPO+, HLA-DR+, CD10-, CD16-, CD13+, CD65+h, CD64+h. Blast 28%

Karyotype: Analyzed 50 metaphases by G-banding and 50 metaphases with DAPI-banding and 5 thousand interphase nuclei with XY sexual sequences. Observed a complex karyotype with significant rearrangements in autosomes and the discovery of an extra X chromosome.

Cytogenomics (FISH) Interphase nuclei with three copies of the RUNX1 gene in 60% and three copies of the CBFB gene are observed in 6%, and in 5% the third copy is deleted towards the 3' end. In addition, 3% of the nuclei carry a normal male diploid pattern and 97% carry an additional X chromosome.

NGS: The sequencing analysis (MySeq, Ilumina) obtained were submitted to the Franklin genomic and clinical data processor (Genoox), with filters for germline and somatic classification. In this way, 7 variants were evident (Tier1, pathogenic and Tier 2, undetermined variables) of 6 genes (*NRAS, ASXL1, ETV6, SETBP1, CEBPA, GATA2*). The 7 variants are recognized as single nucleotide polymorphisms (SNP) and are described in Table 1. Two variants present high confidence with a VAF of 45% and 51% classified as germline and somatic variants.

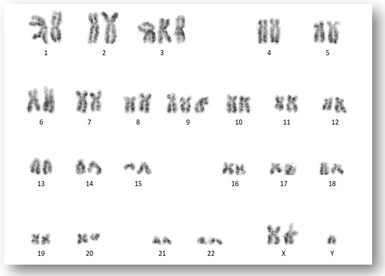


Figure 1. Karyotype: 49,XXY, +3, +9,add (9)(p12), del(11)(q11::q21), del(12)(q24), del(15)(q22),del(20)(q12).

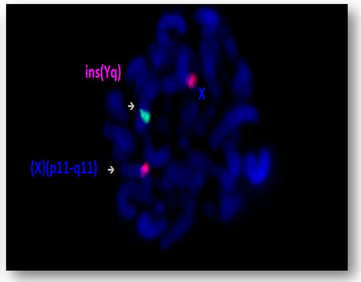


Figure 2. FISH der(11) t(Y:11)(q11-12;q12-q13), (Xp11.q11x2)

Tier 1 P	NRAS p.G12C	FREQUENCY N/A	INTERNAL 1.63% 2 Cases	VAF 45.03% Depth: 1772	CONFIDENCE High Quality:1,968.96	EVIDENCE Ther. A 18/18 Diag. A 3/5 Prog. A 8/9
Chr1:115258748-C-A | NM_002524.5 | c.34G>T | Exon 2						
★ We found 4 Variant articles						
Tier 1 LP	ASXL1 p.G645Vfs*58	FREQUENCY <0.01%	INTERNAL 67.48% 83 Cases	VAF 1.50% Depth: 9268	CONFIDENCE Medium Quality:40.1	EVIDENCE Ther. / 0/0 Diag. A 3/3 Prog. A 6/10
Chr20:31022441-AG-A | NM_015338.6 | c.1934del | Exon 13						
Tier 1 LP	ETV6 p.Q118*	FREQUENCY N/A	INTERNAL 2.44% 3 Cases	VAF 1.03% Depth: 2722	CONFIDENCE High Quality:327	EVIDENCE Ther. / 0/0 Diag. / 0/0 Prog. A 1/1
Chr12:12006384-C-T | NM_001987.5 | c.352C>T | Exon 4						
★ Possibly a germline variant						
Tier 2 VUS	SETBP1 p.S973T	FREQUENCY <0.01%	INTERNAL 0.81% 1 Cases	VAF 51.73% Depth: 2163	CONFIDENCE High Quality:3,178.65	EVIDENCE Ther. / 0/0 Diag. / 0/0 Prog. B 1/1
Chr18:42532223-G-C | NM_015559.3 | c.2918G>C | Exon 4						
Tier 2 VUS	CEBPA p.A94P	FREQUENCY N/A	INTERNAL 80.49% 99 Cases	VAF 1.65% Depth: 11857	CONFIDENCE High Quality:316	EVIDENCE Ther. ? 1/1 Diag. / 0/0 Prog. B 1/1
Chr19:33793041-C-G | NM_004364.5 | c.280G>C | Exon 1						
Tier 2 VUS	CEBPA p.G96=	FREQUENCY N/A	INTERNAL 84.55% 104 Cases	VAF 1.81% Depth: 11852	CONFIDENCE High Quality:321	EVIDENCE Ther. ? 1/1 Diag. / 0/0 Prog. B 1/1
Chr19:33793033-G-C | NM_004364.5 | c.288C>G | Exon 1						
Tier 2 VUS	GATA2 Intronic	FREQUENCY N/A	INTERNAL 86.18% 106 Cases	VAF 1.28% Depth: 1246	CONFIDENCE Medium Quality:176	EVIDENCE Ther. B 1/1 Diag. / 0/0 Prog. / 0/0
Chr3:128200592-T-C | NM_032638.5 | c.1143+70A>G | Exon 5						

Table 1: NGS MySeq Ilumina, identify *NRAS, SETPB1, EZH2, ASXL1, ETV6, CEBPA and GATA2*

CONCLUSIONS

-KS is the most common sex chromosome disorder, associated with an increased risk of various malignancies, an aggressive clinical course, and a low response rate to treatment.
-Currently, there is no standard treatment, but etoposide appears to be effective.
-The previous use of etoposide in germ cell tumors decreases the likelihood of response when used in AML.
-Due to the underdiagnosis of KS and the lack of cohort studies, the risk and association between various neoplasms are unknown.
-Studies are needed to develop combined treatment strategies that achieve a response for both neoplasms.

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