

A RARE AGGRESSIVE HISTIOCYTIC SARCOMA CASE: GENETIC CHARACTERIZATION AND MOLECULAR PATHOLOGY

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ABSTRACT

Herein, a case for histiocytic sarcoma, a rare aggressive type of sarcoma, of a Saudi male patient is presented. NextGen sequencing (NGS) was utilized to assess for mutations in an ethylenediamine tetraacetic acid (EDTA) blood sample of the patient that revealed nine rare variants for three genes namely PIK3CA (phosphatidylinositol-4, 5-bisphosphate,3-kinase catalytic-subunit α ; KRAS(Kirsten rat sarcoma-viral oncogene-homolog); and TP53(tumor protein-p53). This insight into this case can shed a light on potential genes that play impact in pathogenesis/progression of this rare case.

Key-words: Histiocytic sarcoma, next-generation sequencing (NGS), molecular pathology, genetic characterization, gene variants

INTRODUCTION

Histiocytic sarcoma is an aggressive and rare type of sarcoma that arise from histiocytes (Kushwaha *et al.*, 2022). The origin of histiocytic sarcoma is assumed to arise from myeloid origin due to histological characteristic of mature macrophages/histiocytes. A subset of this type of tumor arises from preexisting hematological malignancy. This form of cancer mainly affects adult population (Kushwaha *et al.*, 2022) with median age of diagnosis around 50 years old. This form of sarcoma presents in various organs including the skin, bone marrow, liver, gastrointestinal tract, lymph nodes and spleen. The etiology of histiocytic sarcoma is not fully understood. Certain risk factors are linked to this disease including exposure to chemicals, toxins, radiotherapy, chemotherapy. These risk factors are associated with increased mutations.

Several research studies have been conducted to fully understand this rare tumor and the underlying molecular mechanisms to develop more potent treatment strategies for this condition (Roloff *et al.*, 2019; Hung and Qian, 2020; Kushwaha *et al.*, 2022; Sood and Mehta, 2022). Genetic studies have identified specific mutations in genes such as BRAF (gene encoding a protein B-Raf), MAP-2K-1, and MAP-3K-1. These may play key role in development/progression in this cancer and targeted therapeutic approaches are currently being explored in clinical studies/trials to assess benefit of inhibition of these mutated pathways in patients. Other studies also linked PI3K/MTOR pathways of signaling.

With the investigations obtained in previous work, very little is known about histiocytic sarcoma, and it remains one of the most aggressive group of histiocytic neoplasms. There is no standard therapy for this condition and regimen of combination chemotherapy that is similar to those used in treatment of non-Hodgkin lymphoma are the usual approaches in treatment despite the lack of evidence. The results and response rate to these regimens are mixed and often patients develop resistance to therapy. Here, a Saudi male diagnosed with left axillary lymph node with features consistent with histiocytic sarcoma case report is presented showing the microscopic, immunohistochemistry and genetic mutations (Sood and Mehta, 2022).

CASE PRESENTATION

A 97 years old Saudi male was consulted in a Makkah hospital, Kingdom of Saudi Arabia (KSA). The patient was presented with enlarged left axillary lymph node measuring 4x2x1 cm with necrotic areas.

An excision biopsy was conducted, and the specimen was sent for pathological examination in formalin. Three areas of the samples were collected and prepared for pathological investigation. Microscopically, sections examined revealed complete lymph node infiltration by large pleomorphic cells along with eccentric nuclei & abundant

eosinophilic cytoplasmic contents. Also, giant cells (multinucleated) and tumorous necrotic regions were observed in lymph node.

Sections were sent for immunohistochemistry investigation of the following markers:

CD68, CD5, CD1a, CKAE1/E3, CD4, CD21, CD19, CD10, S100

The samples showed diffused strong staining for CD68 in all pleomorphic cells and giant cells. Also, there was scattered positivity of CD4. The immunohistochemistry was negative for the rest of the markers. The diagnosis in the pathology report was left axillary lymph node, feature consistent with histiocytic sarcoma.

MATERIALS AND METHODS

The ethical approval was acquired from ethical committee in Umm Al-Qura University. Following the procedure, a consent (written informed) was taken from the mentioned patient and an ethylenediamine tetraacetic acid (EDTA) collected blood sample was taken from the patient. The variants-potentially pathogenic, were confirmed via usage of capillary-sequencing (Cheng *et al.*, 2021). To accomplish this, the respective sample was sent to an NIH testing company-Gene Dx and NextGen sequencing was utilized (Roloff *et al.*, 2019) and achieved fewer than 15 reads sequence for regions. Exon-arrays were incorporated to test for concurrent deletion/duplication for the genes in the panel. Gene specific filtering method was performed for data analysis. The human genome build GRCh37/UCSC gh19 was the base used to probe sequences and locations and MLPA, qPCR, or repeat array CGH analysis was used to confirm for copy number changes. Alterations in the sequence and array-CGH were reported (Canuti *et al.*, 2014) while following respectively the instructions of society for genomic variations in human-HGVS and international-system for cytogenetic human nomenclature-ISCN.

RESULTS

Annotation of variants and gene variants prioritization:

Quality control tests were carried out for the respective samples, as variants with an average depth of coverage within targets below 30x were discarded. As our analysis was mainly for the rare-variants, we defined the putative-variants reported via dbSNP (database for SNP-v138) browser v3.1.2 (gnomAD (broadinstitute.org) (<https://gnomad.broadinstitute.org/>), along with $MAF \geq 0.5\%$.

Candidate genes:

We identified nine rare variants (Table 1) for three genes-PIK3CA, KRAS & TP53 genes with $MAF < 0.05\%$. In the present case, we detected eight rare missense mutations and one stop-gained mutation. Nevertheless, we further filtered the rare variants not falling within coding exons or exon/ boundaries or non-functional using the VEP to expect the deleteriousness & damaging effect of variants by SIFT and Poly-Phen2 (<https://gnomad.broadinstitute.org/>). We found two candidate genes: KRAS (MIM 190070), located at the 12p12.1 locus and TP53 (MIM 191170), located at the 17p13.1 locus (Table 1).

Table 1. *In silico* predictive mutation assessment in the breast cancer (bc) case.

Gene	Variant	Position	dbSNP ID	Alt allele frequency	SIFT (score)	PolyPhen2 (score)	GT
KRAS	c. 35G>C, p.Gly12Ala	12:25398284	rs121913529	4.01e-6	Deleterious-(0.02)	possibly damaging-(0.773)	Het
TP-53	817C>T, p.Arg273Cys	17:7577121	rs121913343	1.20e-5	deleterious-(0)	probably damaging-(0.998)	Het
TP-53	c. 624C>A, p.Asp208Glu	17:7578225	New mutation	-	Deleterious-(0)	probably damaging-(0.999)	Het
TP-53	c. 472C>T, p.Arg158Cys	17:7578458	rs587780068	7.96e-6	Deleterious-(0)	probably damaging-(0.996)	Het
TP53	c.438G>A, p.Trp146Ter	17:7578492	New mutation	-	Stop-gained	-	Het

bc: breast cancer, dbSNP: database for single nucleotide polymorphism (SNP), Alt: alternate, GT: genotype, Het: heterozygous status

Rare variants

In this case, we detected two previously undescribed rare pathogenic variants: c.624C >A, p.Asp208Glu (missense mutation) and c.438G >A, p.Trp146X (stop-gain mutation) (Table 1). Both de novo variants are linked to the TP53 gene in heterozygous statuses. In addition, we identified three previously described variants: two allelic variants, c.817C >T (p.Arg273Cys) and c.472C >T (p.Arg158Cys), linked to the TP53 gene, and one allelic variant, c.35G >C (p.Gly12Ala) linked to the KRAS gene. Interestingly, the ClinVar (clinically relevant variants)-database shows that the KRAS genetic variant (c.35G >C; p.Gly12Ala) is associated with gallbladder cancer, ovary neoplasm, large intestine neoplasm, multiple myeloma, gastrointestinal stromal tumor, and non-small cell lung carcinoma. Moreover, the TP53 variants (c.472C >T, and c.817C >T) were shown (Table 1) to be associated with the syndromes predisposing hereditary cancer.

CONCLUSION

The molecular and genetic pathology investigations reveal that by employing the targeted next-generation sequencing, the recurrent alterations and other genetic alterations are identified in the MAP-kinase for pathogenesis/progression of histiocytic sarcoma (Hung and Qian, 2020; Sood and Mehta, 2022). This highly innovative approach suggests the possible therapeutic targets, and the possibility of uncovering the relevant and promising management of histiocytic sarcoma. Furthermore, the diagnostic impact of flow cytometry (Kushwaha *et al.*, 2022) might also be helpful for the identification of cases with histiocytic sarcoma.

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