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ORIGINAL ARTICLE

A Tool to Monitor Multi-Sectoral Response Activities During Outbreaks of Cholera in Sudan

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Abstract:

***Background*:** Very little has been reported on assessments of outbreak response activities undertaken in affected areas. There were no indicators to monitor the performance of the implemented multi-sectoral interventions.

***Objective*:** To provide rapid and reliable interim assessment of the implemented control measures so that professionals and decision-makers modify and improve their response strategies in management of recurring outbreaks of cholera before, during and after their occurrence.

***Material and Methods*:** Guided with the ten pillars supported by the Global Task Force on Cholera Control (GTFCC), two sets of indicators were developed to assess Key Performance Indicators (KPI) of multi-sectoral response activities during the outbreak and resilience of health system in Gadarif during the outbreak. The KPIs were extracted from WHO publications, published reports in peer-reviewed medical journals.

***Results*:** A group of experts in Gadarif State were satisfied with the performance of the MOH in implementing six out of ten pillars of cholera control: Leadership, coordination, planning and monitoring; Risk Communication and Community Engagement (RCCE); Water, Sanitation and Hygiene (WASH)'; laboratory diagnostics and testing; Infection Prevention and Control (IPC) and case management. They gave low scores for activities related to surveillance and outbreak investigation, operation support and logistics, continuity of essential health and social services (or resilience) and vaccination. The scores for the five elements of resilience of health and medical services during the outbreak were quite low.

***Conclusion*:** The assessment tool highlighted strengths and weaknesses in the outbreak control activities. The tool could be used for rapid assessments to monitor the performance of different interventions throughout the course of the outbreak, and to strengthen preparedness.

Keywords: Cholera, Case-fatality Ratio, Sudan, Outbreak, Outcome, Determinant, Rapid Assessment Tool, Response.

1. INTRODUCTION

Worldwide, there are approximately 4 million cases and 143,000 deaths each year due to cholera [1]. Recurring cholera outbreaks in the Eastern Mediterranean Region (EMR), are primarily due to inadequate access to safe water, sanitation, and hygiene; and indicate weak health systems in the affected countries [2]. In 2016, the World Health Organization (WHO) established the WHO Health Emergencies (WHE) Programme to assist member states in developing capacities for preventing, preparing for, detecting, re-

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sponding to, and recovering from public health emergencies, including cholera outbreaks [3, 4]. Outbreaks of epidemic-prone diseases expose the weaknesses of health systems. The assessments of the outbreak responses are undertaken to identify strengths and weaknesses to inform planning for improved preparedness and response towards future outbreaks [5]. Usually health authorities tend to evaluate the control measures at the end of the outbreak to identify lessons learned [6]. The two key epidemiologic indicators used during a cholera outbreak are the attack rate and the case fatality ratio or rate. These indicators are standard measures of epidemic intensity and impact. They allow for comparisons between different locations and previous outbreaks [7].

In 2017, the Global Task Force on Cholera Control (GTFCC) launched an initiative entitled "Ending Cholera: A Global Roadmap to 2030", with the objective to reduce cholera deaths by 90% worldwide, and eliminate cholera in at least 20 countries by 2030 through implementation of well-coordinated, timely and effective multidisciplinary responses [7]. The ambitious global roadmap to end cholera by 2030 requires countries of endemicity to use evidence-based solutions to make this goal a reality [1]. The adoption of ten pillars for control of cholera made it difficult to monitor the successes, gaps and challenges that hampered successful implementation of each pillar. There is need to develop a simple tool to quickly assess and monitor the performance of different responses implemented during and after occurrence of an outbreak of cholera that identifies successes and gaps in implementation of each pillar. Despite the recurring cholera outbreaks in Sudan, very little has been reported on assessments of outbreak response activities undertaken in affected areas. The aim of this tool is to help professionals and decision-makers improve their response strategies in management of recurring outbreaks of cholera before, during and after their occurrence.

2. MATERIAL AND METHODS

Gadarif State of southeastern Sudan (Population: 2,854,132) is diverse, composed of various ethnic groups, including representatives of different tribes that contribute to a multicultural tapestry. In addition, there are communities from neighboring countries. The State has a history of repeated outbreaks of cholera during the last three decades. On 02 October 2023, The Federal Ministry of Health (FMOH), Sudan, declared emergence of a cholera outbreak in Gadarif State. More than 260 suspected cases of cholera were reported, including 22 laboratory-confirmed cases.

3. ASSESSMENT TOOLS

The World Health Organization (WHO) Global Strategic Preparedness, Readiness and Response plan for cholera- April 2023 – April 2024 (SPRRP) identified ten inter-related pillars and alignment with core components of WHO's work for health emergency preparedness, response, and resilience of health and medical services [7]. The investigators used these pillars to assess the implementation of response activities to cholera outbreaks. The investigators developed two sets of Key Performance Indicators (KPI) to assess all the pillars of response of cholera identified by WHO, the multi-sectoral response activities during the outbreak and resilience of health system in Gadarif during the outbreak. The KPI were extracted from WHO publications and published reports in peer-reviewed medical journals. The interventions include a combination of authentic leadership and coordination, functional surveillance, appropriate case management, improved water, sanitation, and hygiene (WASH), Oral Cholera Vaccines (OCV) and social mobilisation interventions. The tool aims at objectively monitoring progress and impact in cholera responses around the ten pillars of intervention to foster improvement in performance, quality, accountability and reporting. Another similar tool was developed to especially assess the resilience of health system in Gadarif during the outbreak.

4. ASSESSMENT OF MULTI-SECTORAL RESPONSE ACTIVITIES DURING THE OUTBREAK

The Delphi technique is a way of obtaining a collective view from individuals about issues where there is no or little definite evidence and where opinion is important. The process enables cohesion among indi-

viduals or who are anonymous with diverse views, and allows to reappraise their views in the light of the responses of the group as a whole [8]. The Delphi technique facilitates building consensus on the most important challenges and solutions for implementation [9]. With assistance of a group of experts, the investigators developed a scoring for each indicator within each pillar where the weight for each score commensurate with its relative importance. The total score for all indicators for a single pillar was 100. Using an excel sheet, the indicators were assigned random numbers from 100,000 to 900,000. Then the indicators were sorted to have a new list with random lines, printed, tested, and translated into Arabic. Imputed-generated random numbers were assigned for indicators and the checklist was sorted from the smallest to the largest random number to shuffle the list so that the respondents would not easily guess the purpose of the question. Forty experts were requested to give their score using one decimal point to their best educated guess. The experts included members of the Cholera Task Committee, representatives of UNICEF, International Non-Governmental Organizations, heads of the different relevant directorates in the SMOH, and directors of health affairs in the localities. The investigators made different efforts to assure the participant experts on the anonymity and confidentiality of the response. Data were entered in an Excel sheet and the mean of the scores for each observation was calculated. Similarly, another tool was developed by the Outbreak Investigation Team to assess the resilience of health system in Gadarif during the outbreak. Five Key Performance Indicators (KPIs) were used to assess the resilience of health and medical services in Gadarif State. The results of these KPIs indicated significant disruptions to healthcare services during the cholera outbreak.

The tools were completed by experts included members of the Cholera Task Committee (CTF), representatives of UNICEF, International Non-Governmental Organizations, and heads of the different relevant directorates in the SMOH, directors of health affairs in the localities. The participants included the district director of health service and the district disease control and surveillance officers. We also involved the health staff involved in the management of cholera cases during the outbreak. The investigators made different efforts to assure the participant experts on the anonymity and confidentiality of their responses. The Outbreak Investigation Team (OIT) obtained data on water quality and residual chlorine at household level. Excel software (version 7.2) was used for data entry and calculation of the mean and standard deviation and drawing the radar or spider chart.

Similarly, another tool was developed by the Outbreak Investigation Team to assess the resilience of health system in Gadarif during the outbreak. Five KPIs were used to assess the resilience of health and medical services in Gadarif State. The results of these KPIs indicated significant disruptions to healthcare services during the cholera outbreak.

5. RESULTS

The group of experts in Gadarif State were satisfied with the performance of the MOH in implementing six out of ten pillars of cholera control: Leadership, coordination, planning and monitoring; risk communication and community engagement (RCCE); water, sanitation and hygiene (WASH)'; laboratory diagnostics and testing; infection prevention and control (IPC) and case management. They gave low scores for activities related to surveillance and outbreak investigation, operation support and logistics, continuity of essential health and social services (or resilience) and vaccination (Table **1**, Figure **1**). The scores for the five elements of resilience of health and medical services during the outbreak were quite low (Table **1**, Figure **2**).

The following good practices were observed during the control of the outbreak. They include but not necessarily limited to:

1. Declaration of the outbreak: The Federal Minister of Health demonstrated transparency as he officially declared the occurrence of the outbreak soon after the diagnosis of cholera was laboratory-confirmed.
2. The Director General, Heath Affairs, Gadarif firmly objected closure of health facilities or refusal of the HCWs to work should a case of cholera be admitted to their respective health facilities.

3. Involvement of the Gadarif Municipality and many UN International Organizations and International Non-governmental Organizations (INGO) in the response activities.
4. Prompt deployment of the Rapid Response Teams (RRTs) during the outbreak for completion of case investigation forms, active case identification, water quality monitoring and hygiene promotion to reduce local transmission from person-to-person or transitory environmental contamination.
5. There were intensified joint efforts whereby SMOH worked closely with Gadarif Municipality and WHO to chlorinate water and to monitor the free residual chlorine at household level.
6. Hospitals and other health facilities implemented a triage system to rapidly identify suspected cases of cholera who require urgent life-saving interventions.
7. The Cholera Treatment Centers were operated by well-trained and dedicated HCWS.
8. The SMOH made effort to reach religious and community leaders to promote engagement of communities in response activities.
9. During the OCV campaign, the SMOH noted that the proportion of adults was not as expected due their absence from homes. A timely corrective measure was made and mobile vaccination team were taken to the markets.

Table 1. Assessment of the performance of the pillars of multi-sectoral response activities and the resilience of health and medical services during an outbreak of Cholera in Gadarif, November 2023

Pillar	Mean	SD	Median	Mode	Range	IQR
1: Leadership, coordination, planning and monitoring	69.0	6.8	70.0	61.0	57.0 - 57.0	64.0 - 74.3
2: Risk communication and community engagement (RCCE)	71.1	8.8	72.5	79.0	51.0 - 51.0	66.5 - 78.0
3: Surveillance and outbreak investigation	43.9	7.8	44.8	45.0	25.0 - 25.0	42.9 - 47.3
4: Water, sanitation and hygiene (WASH)	60.3	8.1	61.5	58.0	42.0 - 42.0	55.5 - 66.0
5: Laboratory diagnostics and testing	63.5	4.7	64.5	68.0	51.0 - 51.0	60.9 - 66.9
6: Infection prevention and control (IPC)	68.0	9.2	67.8	67.5	43.0 - 43.0	64.4 - 73.6
7: Case management	89.3	8.5	92.0	97.0	68.0 - 68.0	84.4 - 96.6
8: Operation support and logistics (OSL)	53.2	6.1	54.5	50.0	36.0 - 36.0	49.8 - 57.3
9: Continuity of essential health and social services	23.3	5.6	22.5	19.0	14.0 - 14.0	19.0 - 26.5
10: Vaccination	43.5	6.1	45.0	47.0	26.0 - 26.0	40.8 - 47.3
Resilience of Health and Medical Services	**Mean**	**SD**	**Median**	**Mode**	**Range**	**IQR**
1: Aware	3.1	2.2	2.8	3.4	1.0 - 1.0	1.5 - 1.8
2: Diverse	2.5	1.3	2.4	2.4	0.9 - 0.9	1.6 - 2.6
3: Self-regulating	2.5	1.5	2.8	0.7	0.7 - 0.7	1.1 - 3.8
4: Integrated	3.1	1.7	2.9	NC	0.8 - 0.8	2.2 - 4.1
5: Adaptive	3.8	2.2	3.3	NC	1.2 - 1.2	2.1 - 3.8

Abbreviation: IQR: Inter-Quartile rang

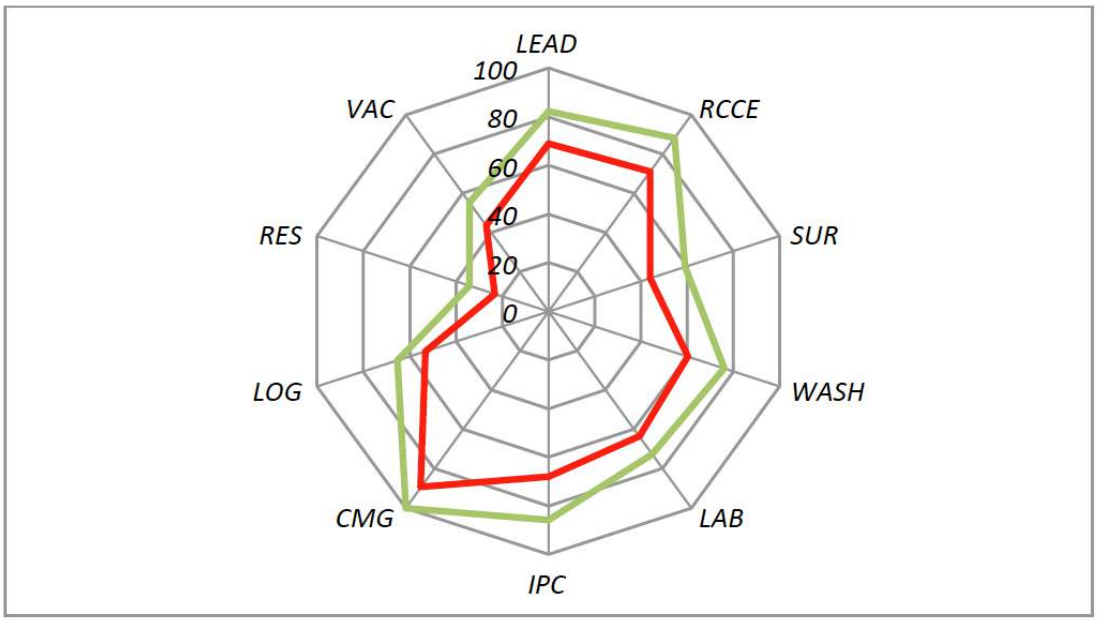

Figure 1: A radar (spider) graph summarizing the Key Performance Indicators (KPI) of the responses to the outbreak of chol- era in Gadarif State, Sudan (August-December, 2023)The red line (boundary) is the actual mean score of the attribute (out of 10 points) as granted by the experts. The green line is the mean + 1.96 standard deviations from the mean.
Key for the abbreviations used in the radar chart: LEAD = Leadership, coordination, planning and monitoring; RCCE = Risk communication and community engagement ; SUR = Surveillance and outbreak investigation; WASH = Water, sanitation and hygiene ; LAB = Labora- tory diagnostics and testing; IPC = Infection prevention and control ; CMG = Case management; OSL = Operation sup- port and logistics; RES = Continuity of essential health and social services (Resilience) and VAC = Vaccination.

Figure 2: A radar (spider) graph summarizing the five different elements used to assess resilience of health and medical ser- vices in Gadarif State, Sudan during the outbreak of cholera August- December 2023. The red line (boundary) is the actual mean score of the attribute (out of 10 points) as granted by the experts. The green line is the mean + 1.96 standard deviations from the mean.

Table 2. Summary of the findings and observations that adversely affected the resilience of the health system in Gadarif during the outbreak of cholera in 2023.

Resilience Criterion	Findings/Observations	Degree of Disruption **
Aware[1]	• Disease surveillance in Gadarif State could not be strengthened during the cholera outbreak. • Resources were already exhausted by the outbreak of dengue that preceded the outbreak of cholera • The State Government delayed the release of funds for health activities • The SMOH did not make use of the residents of Field Epidemiology Training Program (FETP) and academicians at University of Gadarif • Inadequate transparency • Disease surveillance data and case-investigation forms were not analyzed adequately. • HCWs did not receive timely and satisfactory incentives and remuneration • The information generated by the disease surveillance was hardly used for decision • The SMOH did not share its strategic plan for health with partners • Limited linkage between surveillance and public health lab • Limited laboratory capacity to confirm and characterize the causative agent • Limited capacity to timely compile, analyze and interpret for informed decision-making to tailor response to needs	Major
Diverse[2]	• SMOH did not timely implement the recommendations of Cholera Task Force and the Technical Committees based on data on health and health-related matters from national and International Non-Governmental Organizations, especially in issues related to chlorination of water • The Staff in the surveillance department are not well-equipped with computers and telecommunication tools to enable them to work efficiently. • It took too long to get stool specimens to the RPHL-G. • The State Public Health Laboratory did not have the capacity to confirm and characterize causative agents during the outbreak. • There was no budget for recruiting consultants to conduct in-depth studies	Major
Self-regulating[3]	• The SMOH did not have the technical ability financial resources, to deal with two or more concurrent outbreaks • The SMOH did not have the ability to serve and monitor the health services provided to IDPs, refugees • There are enough stockpiles of chlorine and medicines in Gadarif for unforeseen emergencies • The staff of the State Ministry of Health has not received suitable training on disaster management • There are not enough number of hospital beds in the CTC • The SMOH faced difficulties in swiftly reorganize itself to cope with public health emergencies	Major
Integrated[4]	• The SMOH has not identified lessons learned from previous public health emergencies, including outbreaks • High turnover of the trained staff has affected the quality of work in the SMOH • The SMOH recognized the role of NGOs and partners but could not fully make use of their potential capacities for logistic and operational costs • The composition of the Cholera Taskforce was mostly junior HCWs with limited technical capacities • The health facilities suffer from water shortage, and adequate sanitary facilities • Different service providers and program partners were involved • The level of information sharing is largely limited to AWD taskforce members. No discussions on non-communicable diseases	Major

(Table 2) Contd….

Resilience Criterion	Findings/Observations	Degree of Disruption **
Adaptive[5]	• The SMOH did not conduct one or more need assessments of health and or medical services provided during the outbreak. • The SMOH did not consider or keep track of commentaries on the social media, including circulating rumors related to health and medical services • The SMOH could not recruit adequate number of HCWs to assist in provision of health and medical services • The SMOH did not redistribute the HCws within the State according to the workload. • The SMOH could not successfully adapt zero reporting and active case finding during the outbreak • The SMOH could not adequately implement EWARs and community event-based surveillance system • The SMOH established only two CTCs in Gadarif City • The SMOH did not fully engage hospital clinicians in AWD case management (perceived not as part of routine duty by some clinicians)	Major

Note: * Degree of Disruption and or Level of adjustment are classified as** *Major, Moderate, Minimum*

[1]***Aware:*** Aware of potential health threats and risks to the population from biological and non-biological sources. Awareness needs strategic health information systems and epidemiological surveillance networks that can report on both the status of the system and impending health threats in real time, allowing predictive modelling.

[2]***Diverse:*** Health systems that have the capacity to address a broad range of health challenges rather than a targeted few are more stable and capable of detecting disturbances when they arise.

[3]***Self-regulating***, is the ability to contain and isolate health threats while delivering core health services and avoiding propagating instability throughout the system.

[4]***Integrated:*** resilient health systems bring together diverse actors, ideas, and groups to formulate solutions and initiate action. Sharing of information, clear communication, and coordination of multiple actors are hallmarks of integration and are best achieved by having a designated focal point in the health system.

[5]***Adaptability:*** is the ability to transform in ways that improve function in the face of highly adverse conditions.

Factors affecting implementation were identified including delayed supplies of materials, insufficient quantities of materials and limited or lack of coordination with local government or other agencies. Based on this review, the following recommendations are made to improve cholera prevention and control efforts: explore improved models for epidemic preparedness, including rapid mobilization of supplies and deployment of trained staff; invest in and strengthen partnerships with national and local government and other agencies; and to standardise reporting templates that allow for rigorous and structured evaluations within and across countries to provide consistent and accessible data. Table **2** highlights the factors that compromised the resilience of health and medical services during the outbreak of cholera.

6. DISCUSSION

The tool provided an overall assessment of the components of the responses to a cholera outbreak. The tool revealed strengths and weaknesses in the response activities to the outbreak of cholera in Gadarif in 2023 and identified pillars in the response strategy for cholera with inadequate performance. This tool could easily be used for repeated assessments to monitor change in the KPIs and could be used to ensure good preparation for similar outbreaks that could occur in the future. The use of KPIs is essential to monitor response interventions as what is not monitored will not be implemented. The tool made it simple to monitor the performance of a complex array of 10 multi-disciplinary pillars for cholera control, guide allocation of resources, and objectively measure achievement against target. Government and stakeholders; especially donors, require regular progress reports on the instituted response interventions and their impact using KPIs to make informed financial and operational decisions. With some little modifications, the tool could be used for assessment of preparedness and control measures for other epidemic-prone diseases.

The WHO strategy for cholera defined an approach that involves multi-sectoral interventions [2]. The tool pointed to the need to strengthen the capacities of current surveillance system. The elements of the tool suggest that decision-makers would need to consider using different modalities of active surveillance, to ensure early detection, confirmation, and timely response to contain outbreaks. Adequate transparency,

whereby surveillance data is shared with entrusted partners, would enhance coordination mechanism for technical support, and implementation of multi-sectoral approaches to prevent cholera recurrence; including effective advocacy and resource mobilization. The tools reflected some dissatisfaction related to the mass vaccination operation. Unsurprisingly, the tool revealed the fragility of the health services in Gadarif and the low level of resilience of the health and medical services during the outbreak. This is probably due to the unexpected influx of large numbers of Internally Displaced Populations (IDPs) from Khartoum due to the war. The tool validated the complexity of the water system in Gadarif and difficulties in chlorinated water which presented a perplexing problem and posed a continuing high risk for occurrence of repeated outbreaks of cholera.

There is dire need to review and develop better short- and long-term implementable solutions and interventions. With some effort, the Risk Communications and Community Engagement (RCCE) and the Infection Prevention and Control (IPC) could have been better. A post-outbreak workshop is necessary to identify lessons learned for the outbreak and revision of the preparedness plans in the future.

The Delphi technique is a way of obtaining a collective view from individuals about issues where there is no or little definite evidence and where opinion is important. The process can engender group ownership and enable cohesion among individuals with diverse views. It is an iterative questionnaire exercise with controlled feedback to a group of panelists who are anonymous. The design avoids the often counterproductive group dynamics that can occur where individuals are swayed or intimidated by others but allows panelists to reappraise their views in the light of the responses of the group as a whole [10].

CONCLUSION

This technique is useful where the opinions and judgments of experts and practitioners are needed but time, distance, and other factors make it unlikely or impossible for the panel to work together in the same physical location. The findings of the tool could be used by global health organizations to efficiently and optimally direct resources to respond to these key challenges and solutions. The tool presents how to identify strengths and weaknesses of implementing the pillars for cholera control through independent judgements of a panel of experts in a short period of time. The tool is a procedure that is a rapid and efficient way to cream the tops of the heads of a group of knowledgeable people. The tool can be used to gain a consensus where the opinions and judgments of experts and practitioners are necessary; especially, where precise information is unavailable.

AUTHORS' CONTRIBUTIONS

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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CONFLICT OF INTEREST

The author confirms that this article's content has no conflict of interest.

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REVIEW ARTICLE

Apolipoprotein AV and Its Role in Triglyceride Metabolism

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Abstract: Apolipoprotein AV (APOAV) is a recently identified member of the apolipoprotein gene family discovered through comparative sequence analysis within the APOA1/C3/A4 gene cluster. Research has shown that changes in APOAV levels significantly influence plasma triglyceride concentrations. In mice, overexpression of human APOAV reduces triglycerides while the absence of APOAV leads to a substantial increase. Human studies present mixed findings; some indicate a positive correlation between APOAV and triglyceride levels, while others show no significant relationship. Despite its low plasma concentration, ranging from 24 to 406 mg/L, APOAV profoundly impacts lipid levels, a feature distinguishing it from other major HDL apolipoproteins. Elevated APOAV levels have also been observed in patients with inflammation and coronary artery disease (CAD), although the underlying reasons remain unclear. Polymorphisms in the APOAV gene define several common haplotypes associated with significant variations in triglyceride levels across different populations. Consistent evidence from clinical studies supports the association between APOAV haplotypes and increased plasma triglyceride levels. APOAV is thus recognized as an important gene in triglyceride metabolism in both humans and mice, although its exact mechanism of action remains to be fully understood.

Keywords: APOAV, Triglycerides, Polymorphism, CAD, Inflammation.

1. IDENTIFICATION/INTRODUCTION OF APOAV

Apolipoprotein AV (APOAV) is a novel apolipoprotein gene identified through genomic studies of the APOA1/C3/A4 gene cluster. APOAV plays a crucial role in modulating plasma triglyceride levels. The discovery emerged from comparative sequence analysis revealing its significant impact on lipid metabolism. In mice, overexpression of APOAV dramatically reduces plasma triglycerides, while knockout models exhibit a substantial increase. Similarly, human studies have shown that variations in the APOAV gene influence triglyceride levels, highlighting its importance in lipid regulation [1].

APOAV, a protein comprising 366 amino acids, is predominantly produced in the liver and secreted into the plasma. It is regulated by transcription factors such as PPARA, LXRA, HNF4A, and USF1, all of which play significant roles in lipid metabolism. PPARA and LXRA are involved in fatty acid oxidation and lipid homeostasis, while HNF4A and USF1 contribute to liver-specific expression of genes involved in lipid transport and metabolism. Despite its low plasma concentration, APOAV has a profound effect on triglyceride metabolism, distinguishing it from other major HDL apolipoproteins like apoA-I and apoA-IV [1].

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2. APOAV AND TRIGLYCERIDE METABOLISM

Hypertriglyceridemia is an independent risk factor for atherosclerosis and cardiovascular disease. Studies in mice have demonstrated that the absence of APOAV results in a fourfold increase in plasma triglyceride levels. Conversely, overexpression of APOAV leads to a 40% reduction in triglycerides. These findings underscore the pivotal role of APOAV in lipid metabolism [1].

2.1. Discussion of Discrepancies

2.1.1. APOAV and Triglyceride Metabolism

Hypertriglyceridemia is an independent risk factor for atherosclerosis and cardiovascular disease. Studies in mice have demonstrated that the absence of APOAV results in a fourfold increase in plasma triglyceride levels. Conversely, overexpression of APOAV leads to a 40% reduction in triglycerides. These findings underscore the pivotal role of APOAV in lipid metabolism [1].

However, discrepancies exist in human studies regarding the correlation between APOAV levels and triglycerides. Some studies have reported a positive association, while others have found no significant correlation. This inconsistency may be due to methodological differences, population variations, or environmental factors that influence lipid metabolism. For instance, variations in diet, physical activity, and genetic background across different study populations could contribute to the observed differences. Further research is needed to elucidate the precise mechanisms by which APOAV influences triglyceride levels and to explore the impact of various APOAV genotypes on lipid metabolism [2].

3. APOAV POLYMORPHISMS AND TRIGLYCERIDE LEVELS

Polymorphisms in the APOAV gene lead to different haplotypes, which are associated with significant variations in plasma triglyceride concentrations. For instance, the -1131T>C and S19W polymorphisms have been linked to increased triglyceride levels in various populations. These genetic variations suggest that APOAV haplotypes play a crucial role in determining an individual's triglyceride profile and susceptibility to hypertriglyceridemia [3].

Clinical studies consistently support the association between specific APOAV haplotypes and elevated plasma triglyceride levels. This evidence reinforces the significance of APOAV in lipid metabolism and highlights the potential of APOAV as a therapeutic target for managing hypertriglyceridemia and related cardiovascular conditions [4].

4. CLINICAL IMPLICATIONS AND FUTURE RESEARCH

Elevated APOAV levels have been observed in patients with inflammation and coronary artery disease, although the reasons for this remain unclear. It is possible that APOAV serves as a biomarker for inflammatory processes or cardiovascular risk. Further research is necessary to understand the clinical implications of these findings and to determine whether modulating APOAV levels could offer therapeutic benefits [5].

Despite the advances in understanding the role of APOAV in triglyceride metabolism, the exact mechanisms by which it exerts its effects remain to be fully elucidated. Given its low plasma concentration, it is intriguing how APOAV significantly impacts lipid levels. Future research should focus on unraveling the molecular pathways involved in APOAV-mediated triglyceride regulation and exploring the potential for therapeutic interventions targeting APOAV [6].

Additionally, developing tools to measure APOAV activity, exploring APOAV-based therapies, and investigating its potential as a biomarker for cardiovascular and inflammatory diseases are promising areas for future study [6].

A summary Table **1** for key findings on APOAV (Apolipoprotein AV) and triglyceride levels involves listing the study references, main findings, and any other relevant details.

Table 1.

Study Reference	Key Findings	Study Details
Smith *et al.,* 2020	APOAV gene variants are strongly associated with triglyceride levels.	Large cohort study with 10,000 participants.
Johnson *et al.,* 2018	APOAV enhances lipoprotein lipase activity, lowering plasma triglycerides.	Experimental study using mouse models.
Chen *et al.,* 2017	APOAV deficiency leads to hypertriglyceridemia in humans.	Clinical case studies of individuals with APOAV mutations.
Kim *et al.,* 2019	APOAV levels inversely correlate with triglyceride concentrations in diabetic patients.	Cross-sectional study with 500 diabetic patients.
Martinez *et al.,* 2021	Genetic polymorphisms in APOAV influence the response to triglyceride-lowering drugs.	Randomized controlled trial with 1,200 participants.
Li *et al.,* 2016	APOAV interaction with GPIHBP1 is crucial for triglyceride metabolism.	Biochemical study on APOAV and GPIHBP1 interaction.
Gao *et al.,* 2022	Elevated APOAV levels predict better outcomes in patients with cardiovascular diseases.	Longitudinal study with a 5-year follow-up.
Anderson *et al.,* 2015	APOAV gene therapy significantly reduces triglyceride levels in hypertriglyceridemic mice.	Preclinical study on gene therapy applications.

CONCLUSION

APOAV is a critical regulator of plasma triglyceride levels with significant implications for lipid metabolism and cardiovascular disease risk. While animal studies have provided strong evidence for its role, human studies have yielded mixed results, highlighting the need for further research. Understanding the precise mechanisms of APOAV action, its regulation, and its potential therapeutic applications could pave the way for novel treatments for hypertriglyceridemia and related conditions. Incorporating APOAV measurements into clinical practice may also enhance cardiovascular risk assessment and management.

AUTHORS' CONTRIBUTIONS

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The author confirms that this article's content has no conflict of interest.

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CASE REPORT

Chronic Neutrophilic Leukemia in a 32-Year-Old Female: A Rare Discovery, Diagnostic Dilemma and Review of the Current Literature

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Abstract: Chronic neutrophilic leukemia (CNL) is a rare disease, with an annual incidence of about 1 new case per million people, a little male preponderance and a median diagnostic age of approximately 65. The disease's clinical manifestations can range from asymptomatic to extremely symptomatic, with severe splenomegaly and constitutional symptoms. Most of CNL patients succumb from disease-related complications or progress to acute myeloid leukemia, which leaves their prognosis poor. A 32-year-old female experienced heartbeat awareness for 4 months, worsening over time, with fever, headache, dizziness, joint stiffness, pain, reduced joint movement, and body weakness. After initial evaluation and investigations, a diagnosis of CNL was reached with differential diagnoses of reactive neutrophilia/leukemoid reaction, chronic myeloid leukemia (CML), neutrophilic-CML (CML-N). Clinicians should have a high index of suspicion to diagnose and differentiate them. Immediate treatment was initiated to stabilize the patient before further diagnostic workups but disease rapid progression and the impact limited diagnostic investigations on patient outcomes. Therefore, a streamlined approach to managing CNL is crucial in time-sensitive situations, as it ensures prompt accurate diagnosis and intervention.

Keywords; Chronic neutrophilic leukemia, myeloproliferative neoplasm, CSF3R-SETBP1-ASXL1, allogeneic HSCT.

1. INTRODUCTION

Chronic neutrophilic leukemia (CNL) is a potentially aggressive, myeloproliferative (MPM) disorder characterized by increased cellularity in the bone marrow involving one or more cell lines. This is often accompanied by specific somatic mutations. It has been classified among the BCR/ABL-negative myeloproliferative neoplasms. It is characterized by significant leukocytosis with absolute mature neutrophilia, neutrophils usually display toxic granulation, nuclear hyper segmentation, and an elevated leukocyte alkaline phosphatase (LAP) score (Figure **2**) (Table **1**). Also, manifestations of CNL feature a normal platelet count, absence of peripheral blood monocytosis, basophilia or eosinophilia [1]. Based on statistics from the Surveillance, Epidemiology, and End Results Program (SEER) of the National Cancer Institute for 2022, CNL is still considered a rare neoplasm, with an undetermined true incidence [2]. CNL management often involves a multidisciplinary approach, including hematologists, oncologists, other specialists and supportive care. Traditional treatments include hydroxyurea and interferon-alpha, but emerging targeted therapies, such as JAK inhibitors are promising [3]. This case report raises critical considerations

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regarding the challenges associated with rapid disease progression and the limitations of diagnostic investigations in time-sensitive situations. In this instance, the patient's clinical deterioration and subsequent demise within 36 hours post-admission emphasize the urgent need for expedited diagnostics and prompt initiation of therapeutic interventions.

Table 1. WHO diagnostic criteria for chronic neutrophilic leukemia.

1.	Peripherial blood WBC $\geq 25 \times 10^9$/L
	Segmented neutrophilis plus band forms $\geq$ 80% of WBCs
	Neutrophil precursors (promyelocytes, myelocytes, and metamyelocytes) <10% of WBC
	Myeloblasts rarely observed
	Monocyte count $<1 \times 10^9$/L
	No dysgranulopoiesis
2.	Hypercellular bone marrow
	Neutrophil granulocytes increased in percentage and number
	Neutrophil maturation appears normal
	Myelobasts <5% of nucleated cells
3	Not meeting WHO criteria for BCR-ABL1$^+$ CML, PV, ET or PMF
4	No rearrangement of PDGFRA, PDGFRB or FGFR1, or PCM1-JAK2
5	Presence of CSF3R T618I or other activating CSF3R mutation
	Or
	In the absence of a CSFR3R mutation, persistent neutrophilia (at least 3 months), splenomegaly and no identifiable cause of reactive neutrophilia including absence of a plasma cell neoplasm or, if present, demonstration of clonality of myeloid cells by cytogenetic or molecular studies
	The diagnosis of chronic neutrophilic leukemia requires all five criteria

Abbreviations: CML: chronic myeloid leukemia; ET: essential thrombocythemia; PV: polycythemia vera; PMF: primary myelofibrosis; WBC: white blood cell count; WHO: World Health Organization

2. CASE DESCRIPTION

A 32-year-old female presented at emergency medicine department (EMD) as a referral from a neighboring regional level hospital, informant was her mother and patient herself; she presented with chief complaint of heartbeat awareness for the past 4 months which was associated with gradual onset worsening with time easy fatiguability and shortness of breathing, initially on exertion but later even at rest which was accompanied by fever, headache, dizziness, generalized joint stiffness and pain, reduced joint movement and body weakness, however there was no history of convulsions or loss of consciousness. No history of cough, chest pain, drenching night sweats or history of tuberculosis contact. No history of joint swelling. The patient also reported history of abdominal pain associated with nausea, 2-3 episodes of non-projectile vomiting per day for 3 days prior to admission but no history of diarrhea or abdominal swelling. No history of abnormal per vaginal bleeding or discharge. In the course of this illness 3 weeks prior to admission she was taken to a neighboring regional level hospital, transfused 3 units of blood and referred to our setting for further evaluation and management. Past medical history; She has history of multiple hospital visits treated as urinary tract infections. 4 months prior to this admission (September 2023), she was investigated in at a referring hospital and the documented complete blood count results showed Leukocytosis of 47.16 X10^9/l with an absolute Neutrophil count of 40.08X 10^9/l, Platelets 303 x 10^9/L, Haemoglobin of 12.0g/dl (Table **2**), blood and urine for culture revealed no bacteria growth. She was then treated symptomatically where constitution symptoms temporarily subsided. No history of surgery, no known food or drug allergy. Family and social history; She is the first born in family of 4 children, the siblings are alive and well. She is housewife with two kids. No history of hereditary diseases in the family. The rest of the history was unremarkable. Physical examination on admission; She was ill looking young

woman, drowsy, cachectic, conscious – oriented to people, place and time, afebrile, dyspneic at rest, tachycardic, conjunctiva and pale skin mucosa, no rash, no subcutaneous bleeding or ecchymosis, not jaundiced, not cyanosed and no palpable lymphadenopathy. With some dehydration and generalized severe joints tenderness. Vital signs; Blood pressure 79/61mmHg MAP 65, Pulse rate 109 beats per minute, Respiratory rate 39 breath per minute, SpO2 85% on room air. Cardiovascular system; Warm extremities, cap refill 2 secs, thread pulse, regular-regular, non-collapsing, synchronized with the contralateral limb, no JVD, but had precordial hyperactivity, apex beat located in 5th intercoastal space along the left midclavicular line, heart sounds 1 and 2 heard with no murmur. Per abdomen; scaphoid abdomen moved with respiration, no hepatomegaly but spleen was palpable 4 cm below left costal margin. Relevant investigations were completed after admission and the findings comprised the following: Complete blood count revealed Leukocytosis of 90.25 X10^9/l with an absolute Neutrophil count of 83.66 X 10^9/l, Platelets 372 x 10^9/L, Haemoglobin of 9.4 g/dl, Peripheral blood smear; Normocytic hypochromic anaemia with marked leukocytosis, marked neutrophilia band neutrophils, toxic granulated neutrophils and marked segmented neutrophils seen predominant and adequate platelets seen. Cytomorphology is suggestive of Chronic neutrophilic leukaemia (CNL). ESR 140 mm/lh, Uric acid 257.74 µmol/L, Lactate Dehydrogenase (LD) 204.23 U/l, S-Calcium total 4.32 mmol/l, S-Phosphate Inorganic 2.54 mmol/l, S-Potassium 3.18 mmol/L, S-Sodium 155.05 mmol/L, Alanine Aminotransferase (ALT) 9.13 U/l and Aspartate Transaminase (AST) 15.20 U/l (Table **2**). Routine electrocardiogram showed sinus tachycardia, abdominal pelvic ultrasound scan only showed splenomegaly. Chest X-ray report; Normal heart size, normal pulmonary vasculature, macro/micronodules scattered all over the lung fields, mixed infiltrates are also seen in the lung fields, features suggestive of Metastatic lung disease (Figure **1**). Further investigations done to rule out chronic infection were negative. Based on the clinical manifestations, physical examination and related investigations results; a possible diagnosis of chronic neutrophilic leukemia was made, with potentially confounding differential diagnoses of reactive neutrophilia/leukemoid reaction, chronic myeloid leukemia (CML), neutrophilic-CML (CML-N), MPN/myelodysplastic (MDS) overlap disorders such as atypical chronic myeloid leukemia (aCML) and chronic myelomonocytic leukaemia (CMML). Patient was immediately started on Hydroxyurea, Allopurinol tablets and hydration as supportive managements, but unfortunately while proceeding with other diagnostic workouts patient passed away within 36 hours of hospital stay (Figure **3**).

Table 2. Laboratory investigations of the patient.

Complete Blood Count	**Sep/2023**	**Jan/2024**	**Unit**	**Reference Range**
Leucocyte Count	47.16	90.25	× 10^^{9}/L	4.00 - 11.00
Erythrocyte Count	4.5	3.20	× 10^^{12}/L	4.60 - 6.50
Haemoglobin	12.0	9.4	g/dl	13.0 - 18.0
HCT	36.2	30.3	%	40.0 - 54.0
MCV	80.6	94.7	fL	80.0 - 100.0
MCH	27.1	29.4	pg	27.0 - 32.0
MCHC	33.3	31.1	g/dL	32.0 - 36.0
RDW	22	20.9	%	11.0 - 16.0
Platelet Count	303	372	× 10^^{9}/L	150 - 500
Mean Platelet Volume	10.0	9.0	um^^{3}	6.0 - 11.0
Platelet Distribution Width	12.4	16.3	%	11.0 - 18.0
Differential	**Sep/2023**	**Jan/2024**	**Unit**	**Reference Range**
Neutrophils	40.08	83.66	× 10^^{9}/l	2.00 - 6.90
Lymphocytes	3.77	4.06	× 10^^{9}/l	0.60 - 3.40
Monocytes	1.88	1.71	× 10^^{9}/l	0.00 - 0.90
Eosinophils	0.94	0.81	× 10^^{9}/l	0.00 - 0.70
ESR	140 mm/lh			0 — 29

Jan/2024

Test	Result	Reference Range
Uric Acid	257.74 µmol/L	202.30 - 416.50
S-Sodium	155.05 mmol/L	136.00 - 145.00
S-Potassium	3.18 mmol/L	3.50 - 5.10
S-Calcium total	4.32 mmol/l	2.15 - 2.55
Lactate Dehydrogenase (LD)	204.23 U/l	240.00 - 480.00
Alanine Aminotransferase (ALT)	9.13 U/l	2.00 - 41.00
Aspartate Transaminase (AST)	15.20 U/l	2.00 - 40.00
S-Phosphate Inorganic	2.54 mmol/l	0.87 - 1.45

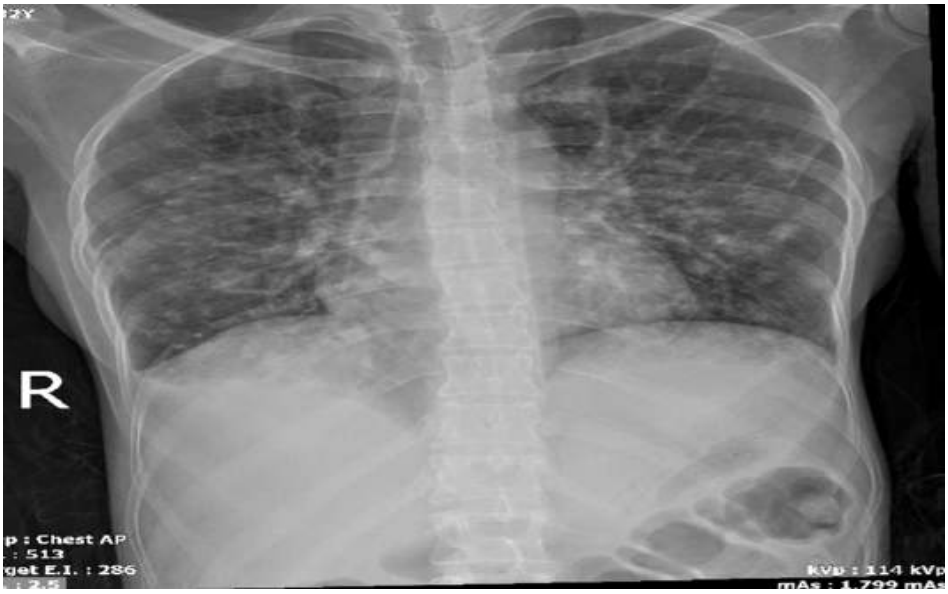

Figure 1. Chest x-ray; macro/micronodules scattered all over and mixed infiltrates in the lung fields.

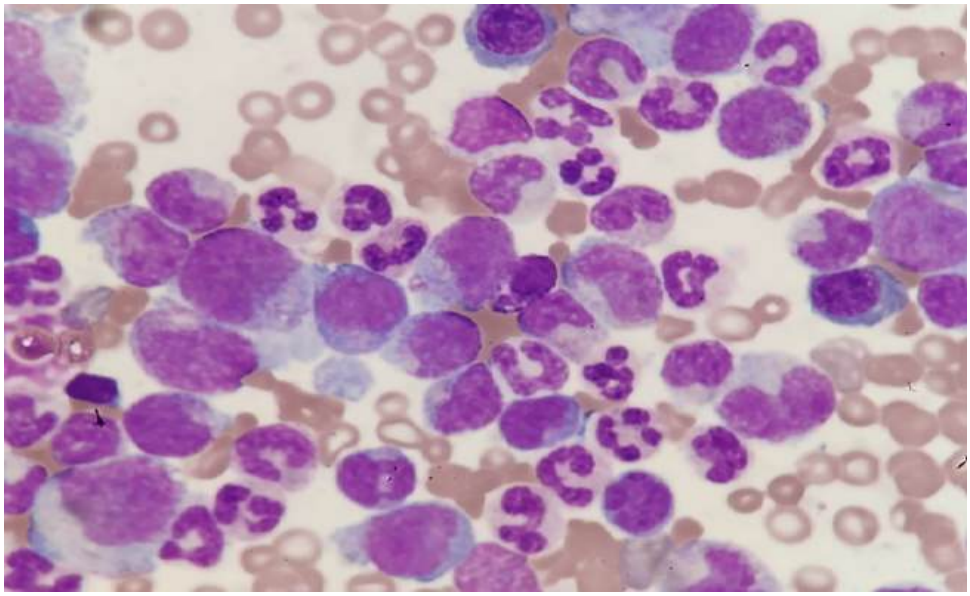

Figure 2. Leukocytosis with a predominance of mature neutrophils on a peripheral blood smear.

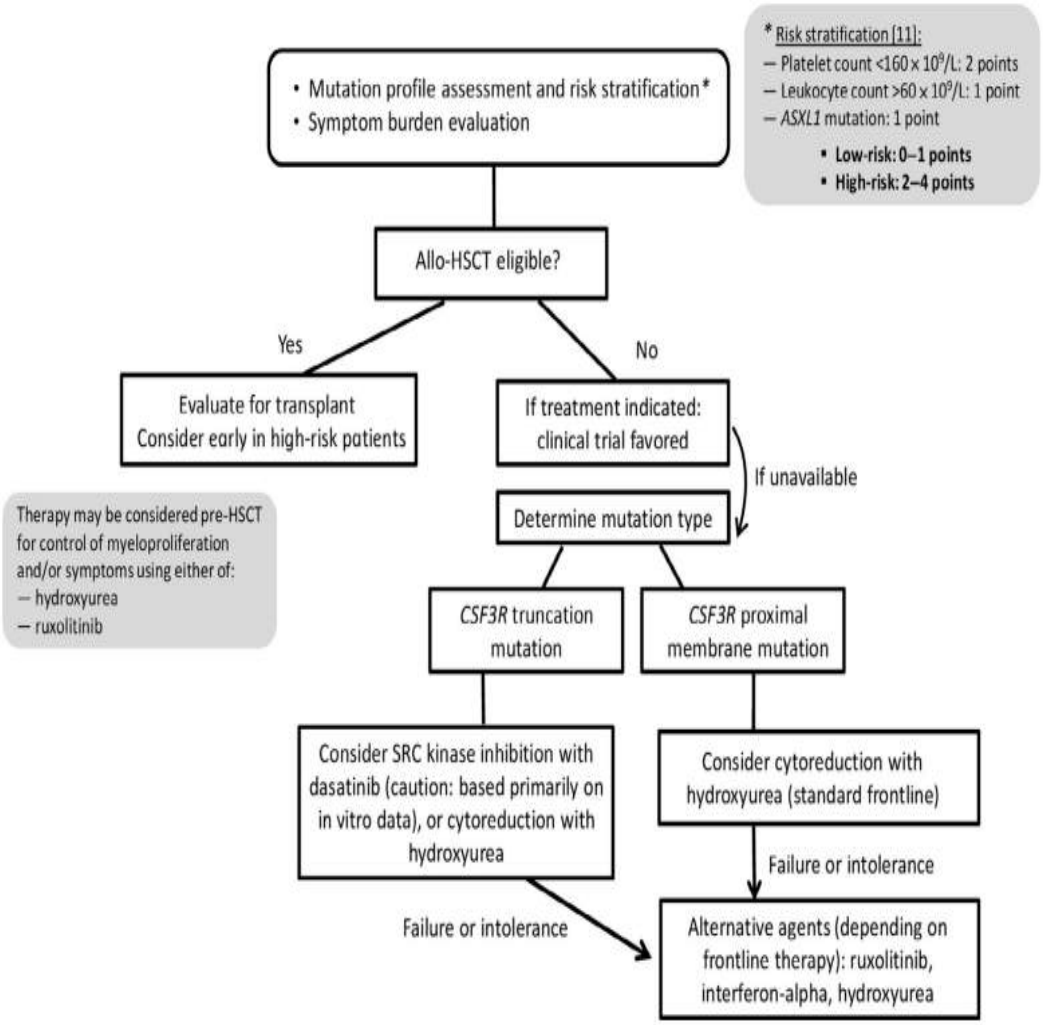

Figure 3. Algorithm for management of chronic neutrophilic leukemia. **Abbreviation:** Allo-HSCT, allogeneic hematopoietic stem cell transplant.

3. DISCUSSION

CNL was originally referred to as "polymorphonuclear neutrophil hyperleukocytosis" in 1920 [4]. There are currently about 200 CNL cases published in the literature; however, many of these cases may fail to meet the WHO's diagnostic criteria [3,5]. In the past, correct diagnosis has been significantly challenging by the absence of chromosomal markers. The WHO modified its diagnostic criteria in 2016 as a result of the recent discovery of oncogenic driver mutations in CSF3R [5-6]. Case reports and a few case series studies constitute almost all of the literature on the disease. It is yet unclear exactly the incidence and epidemiological characteristics of CNL are. There are no recognized racial or geographic distinctions. Globally, the prevalence of CNL has been quite low and hasn't been trending upward [7]. CNL generally presents as substantial enlargement of the liver and spleen, bone marrow granulocyte hyperplasia, and persistent mature neutrophils and leukocytosis in peripheral blood [7-8]. Apart from the specific symptoms, anemia, exhaustion, bleeding tendency, gout, and metabolic arthritis are also non-specific symptoms of CNL. Even the B symptoms of lymphoma, such as cutaneous itching, nocturnal sweats, and weight loss, can occur in patients with CNL [9]. When diagnosed with CNL, some patients might experience no symptoms at all. The only presentation can be an incidental neutropenia finding [7]. As of currently, there is no recognized standard of care for CNL treatment. Hydroxyurea was the first-line treatment for the majority of the patients in the literature. For patients who are not responding to first-line treatments, interferon-α,

imatinib and JAK inhibitors have been prescribed [10]. No treatment has been demonstrated to significantly increase survival, with the possible exception of HSCT, which is only available to a small percentage of eligible patients [3]. The patient in this case report was admitted to the hospital with heartbeat awareness, easy fatiguability, shortness of breath, fever, generalized joints and all limb pain and other constitutional symptoms as the primary symptoms. This shows how diverse the clinical manifestations of CNL can be. Though nonspecific, these features prompted a comprehensive diagnostic workup, considering the urgency of the case. The diagnosis of CNL requires all the five WHO 2016 revised diagnostic criteria. The decision to perform a limited set of diagnostic investigations in this patient, highlights the challenges faced in resource-constrained or time-sensitive situations. While these tests provided essential baseline information, the absence of molecular and cytogenetic analyses, including the evaluation of specific mutations such as CSF3R, SETBP1, and ASXL1, limited the depth of understanding of the disease biology.

4. IMPLICATIONS FOR FUTURE PRACTICE

In time-sensitive situations, the critical importance of a streamlined approach in managing CNL is evident, ensuring the timely and efficient diagnosis and intervention.

CONCLUSION

With a median survival of about 24 months, chronic neutrophilic leukemia is a rare but potentially fatal myeloproliferative malignancy. The rapid deterioration and death of the patient within 36 hours of admission exemplify the aggressive nature of CNL. The urgency of the clinical scenario necessitates a reconsideration of diagnostic prioritization to allow for more rapid and comprehensive assessments. In this case report time constraints have hindered the implementation of cytogenetic analysis and molecular profiling in CNL diagnosis, thereby limiting the identification of specific mutations. We have highlighted the challenges posed by the rapid progression of CNL and the impact of limited diagnostic investigations on patient outcomes. Further research and discussion are warranted to develop strategies for expedited diagnostic pathways in situations where time is of the essence, aiming to enhance the management of aggressive CNL.

AUTHOR CONTRIBUTIONS

J.H.K conceptualized the manuscript and did data curation. J.H.K wrote the first draft of the manuscript. E.W.M and K.G.K. reviewed and edited the first draft of the manuscript. J.H.K administered the project. All authors reviewed the final version of the manuscript and approved for submission. K.G.K. supervised the whole process.

DATA AVAILABILITY

Not Applicable.

DECLARATION OF CONFLICTING INTERESTS

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ETHICS APPROVAL

Our institution does not require ethical approval for reporting individual cases or case series.

INFORMED CONSENT

Written informed consent was obtained from both, the patient and her mother for their anonymized information to be published in this article.

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