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Epidemiology, Management, and Outcome of Atypical Hemolytic Uremic Syndrome in an Omani Cohort

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ABSTRACT

Objectives: Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening disease of chronic uncontrolled complement pathway activation that leads to thrombotic-microangiopathy, along with severe organ damage, including end-stage kidney disease. This study aimed to evaluate the epidemiology, management, and outcome of aHUS in an Omani population. ***Methods***: This retrospective descriptive cohort study assessed all cases of aHUS diagnosed and followed up at two tertiary care centers in Oman from January 2008 to December 2019, based on clinical features, complement pathway assays, histopathological, and genetic testing. ***Results:*** The study accrued 19 patients who fulfilled the inclusion criteria, of whom 11 (57.9%) were male. The participants' median age was 25.0 years (range = 0.1–69.0). Most (15; 78.9%) patients presented in the acute phase of the disease. The triad of hemolytic anemia, acute kidney injury, and thrombocytopenia was present in all patients. A trigger factor (e.g., infection) was identified in 68.4% of cases. Of the 14 (73.7%) patients who underwent kidney biopsy, 10 (71.4%) were found to have aHUS in native kidneys and three in grafted kidneys. Of the 11 (57.9%) patients who underwent genetic analysis, five (45.5%) were found to have a known pathogenic variant in their aHUS susceptibility genes. Plasma exchange followed by eculizumab was the treatment method in 11 (57.9%) cases. Complete renal recovery was achieved in seven (36.8%) patients, while four (21.1%) passed away during the study period. ***Conclusions:*** The wide spectrum and multiple expressions of aHUS make it a challenge to diagnose and consequently may delay the commencement of the targeted treatment. Eculizumab is considered the first-line therapy and should be commenced as early as possible.

Hemolytic uremic syndrome (HUS) is a sporadic disease characterized by hemolytic anemia, sudden or gradual onset of thrombocytopenia, acute kidney injury (AKI), and/or extra-renal end organ damage.[1,2] HUS is indicated by thrombotic microangiopathy (TMA) on histological examination.[3,4] More than 90% of HUS cases are known to be triggered by infection with Shiga-like toxin-producing *Escherichia coli* (STEC-HUS) and carry a good prognosis.[5] On the other hand, patients with non-STEC-HUS tend to have poor prognosis indicators and high morbidity and mortality rates.[6] If left untreated, there is a lifelong risk of kidney dysfunction, end-stage kidney disease, extra-renal complications, and premature death.

We have previously reported that most Omani HUS cases we encountered had associated STEC-HUS infections.[7] We also found the local HUS population to be young, mostly male, and only 25% having known medical comorbidities at the time of presentation. Most of these patients also presented with AKI requiring dialysis, of which peritoneal dialysis was the mainstay of extant therapeutic

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modality. If renal replacement therapy was required, the mean duration and recovery time was almost a month in this population.[7]

Atypical HUS (aHUS) is an aggressive, lethal, and global disease, classified as a rare genetic disorder that stems from an inappropriate stimulation of the complement system.[8] It is termed 'atypical' owing to the absence of an activating event similar to that for the conventional HUS, such as Shiga-like toxin. Though aHUS can occur or manifest at any age, it predominately affects children and young adults.[9]

The fundamental pathophysiology of aHUS is uncontrolled stimulation of the complement pathway, which affects various vascular beds.[10] A quarter of patients succumb to death in the acute phase, and up to half progress to end-stage kidney disease, which is exacerbated by dysregulation leading to glomerular endothelial cell damage.[11] Up to 48% of patients may present with extrarenal manifestations with frequent neurologic and cardiovascular involvements. However, early diagnosis and prompt treatment can improve the prognoses of aHUS patients.[12]

Dysregulation of the alternative pathways of the complement system at various stages is a crucial part of the pathogenesis of aHUS.[13] The complement system, a part of the innate immune system, can be triggered through its three pathways: classical, alternative, and lectin pathways.[4,8,9,11] These three complement tracks congregate at the cleavage and activation of the fundamental complement component 3 (C3) protein. The initiation of the alternative pathway is securely controlled by numerous circulating and cell-bound complement regulatory proteins. Normally, an energy equilibrium exists between complement activation and inactivation.[4,8,9,11] Genetic alterations play a role in such activation, and almost half of the aHUS-affected people carry mutations in complement genes.[13–14] The loss-of-function mutations in regulators such as complement factor H (CFH), complement factor I (CFI), membrane cofactor protein, and thrombomodulin (THBD); and gain-of-function mutations in the key complement components C3 and complement factor B (CFB) increase the vulnerability to aHUS.[13–15] The genotype-phenotype relationships of aHUS have clinical implications for predicting kidney recovery and positive transplant results.[16,17]

It is essential to report validated cases of aHUS cases in as many populations as possible because different populations and ethnicities may have differing responses to the same disease or its triggering factors due to genetic, environmental, and lifestyle variations.[18] There is a dearth of research on aHUS among the populations in the Arabian Gulf countries including Oman. Therefore, this study aimed to retrospectively evaluate the clinical and laboratory findings related to the aHUS cases diagnosed and treated in Oman over an 11-year period.

METHODS

This retrospective descriptive cohort study evaluated cases of all adults and children with the clinical diagnosis of aHUS during the 12-year period from January 2008 to December 2019, who were diagnosed and treated at the country's two main tertiary care centers, the Royal Hospital (RH) and Sultan Qaboos University Hospital (SQUH). Being the only centers in Oman equipped to diagnose and provide comprehensive care for a spectrum of aHUS cases, they receive referrals from all parts of the country.

For this study, HUS was defined by the triad of hemolytic anemia, thrombocytopenia, and AKI; aHUS were suspected in all patients with typical history but with negative stool cultures for Shiga-like toxin and normal ADAMTS13 activity above 10%. We excluded patients with Shiga-toxin-related HUS and secondary TMA. The electronic medical records of patient demographics, clinical characteristics, and laboratory tests including genetic analysis and histopathological tests were extracted from the respective hospital's information system, pertaining to the time of initial presentation, three months thereafter, and at the last follow-up, for renal outcome or death.

As per the protocol followed by SQUH and RH, renal biopsies were submitted for light microscopy, immunofluorescence, and electron microscopy. For light microscopy, hematoxylin and eosin stain, periodic acid-Schiff and Jones silver stain (performed at three levels), and Miller's elastic stain were used. The immunofluorescence panel includes immunoglobulin (Ig) A, IgG, IgM, C3, C1q, kappa, and lambda. The molecular genetic testing is conducted using next-generation sequencing gene panels in Clinical Pathology Accreditation,

College of American Pathologists, and/or Clinical Laboratory Improvement Amendments-accredited diagnostic molecular genetics laboratories as per established protocol.

As per the patient records, the following genes were fully sequenced: *CFH*, *CFI*, *CD46*, *C3*, *CFB*, and multiplex ligation-dependent probe amplification in *CFH*, *CFHR1*, and *CFHR3* (Northern Genetics Service, Newcastle upon Tyne, UK, for four patients). Full gene sequencing, including 10 bp of flanking intronic sequences and deletion/duplication analysis, was included in the analyses of the following genes: *ADAMTS13*, *C3*, *CD46*, *CFB*, *CFH*, *CFHR1*, *CFHR2*, *CFHR4*, *CFHR5*, *CFI*, *DGKE*, *PIGA*, and *THBD* (Fulgent, Temple City, CA, USA, for four patients), and *ADAMTS13*, *C3*, *CD46*, *CFB*, *CFH*, *CFHR1*, *CFHR2*, *CFHR3*, *CFHR5*, *CFI*, *DGKE*, *MMACHC*, *PIGA*, *PLG*, and *THBD* (Cento gene, Rostock, Germany, for three patients).

We have reported the descriptive statistics as frequencies and percentages for categorical variables. Continuous variables were described as median and ranges or as mean and SDs. *P*-values < 0.05 were considered statistically significant. All statistical calculations were performed with the STATA 13 software (version 13.0, Stata Corp, College Station, Texas 77845, USA).

This study was approved by the medical research ethical committees of SQUH and RH (Ref. SQU-EC/153/18MREC1772, RH SRC 58/2018).

RESULTS

The subjects of this study were 19 patients diagnosed with aHUS. All patients were Omani nationals, with a median age of 25.0 years (0.1–69.0). Twelve (63.2%) patients were adults, and 11 (57.9%) were male. None had any family history of aHUS. The majority (78.9%) of the patients presented during the acute phase of the disease. Only four (21.1%) cases had clinical evidence of chronicity at presentation. In 13 (68.4%) patients, a trigger factor was identified. More details are in Table 1.

The frequencies of extra-renal manifestations are shown in Table 2. The central nervous system manifestations included seizure and encephalopathy in six (31.6%) cases each and stroke in two (10.5%) cases. Ocular manifestations (such as optic atrophy) were found in three (15.8%) cases. Cardiovascular

Table 1: Demographic and clinical data of Omani patients with atypical hemolytic uremic syndrome (N = 19).

Demographic data	n (%)
Median age, years	25.0 (range: 0.1–69.0)
Omani nationality	19 (100)
Sex	
Male	11 (57.9)
Female	8 (42.1)
Comorbid disease	
Diabetes mellitus	2 (10.5)
Hypertension	12 (63.2)
Obesity	5 (26.3)
Clinical presentation	
Acute	15 (78.9)
Chronic	4 (21.1)
Trigger factors	13 (68.4)
Infections	11 (84.6)
Gastroenteritis	6 (46.2)
Rickettsia	1 (7.7)
Escherichia coli	1 (7.7)
Upper respiratory tract infection	2 (18)
Mycoplasma plasma	1 (9)
Postpartum	2 (15.4)
Post-kidney transplant	3 (23.1)
Antiphospholipid	1 (7.7)
No trigger factor	4 (30.8)

Table 2: The frequency of clinical and laboratory data of Omani patients with atypical hemolytic uremic syndrome on presentation (N = 19).

Category	n (%)
Clinical data	
Seizure	6 (31.6)
Encephalopathy	6 (31.6)
Stroke	2 (10.5)
Ocular manifestation	3 (15.8)
Cardiopulmonary	2 (10.5)
High blood pressure	12 (63.2)
Diffuse vasculitis	2 (10.5)
AKI	17 (89.5)
CKD	3 (15.8)
Laboratory data	
Anemia	18 (94.7)
Fragmented RBCs (schistocytes)	18 (94.7)
Thrombocytopenia	18 (94.7)
Blood film (toxic granulation)	6 (31.6)
Proteinuria	18 (94.7)
Microscopic hematuria	18 (94.7)

AKI: acute kidney injury; CKD: chronic kidney disease; RBC: red blood cell.

manifestations were found in two (10.5%) cases. Additionally, there was one case with global hyperkinesia suggestive of dilated cardiomyopathy and another one with mitral regurgitation. Elevated liver enzymes were present in five (26.3%) patients. One patient at presentation was found to have liver cirrhosis with portal vein thrombosis. Another patient presented with extensive deep vein thrombosis of the lower extremities. There were no cases of pancreatitis.

Table 3 compares the changes in patient parameters between presentation and three months follow-up. The triad of hemolytic anemia, AKI, and thrombocytopenia was present in most of the cases at the time of presentation. AKI with anemia was present in all cases, with a median creatinine level of 358 umol/L (range = 45–1040) and a median hemoglobin level of 8.0 g/dL (4.1–10.9). All patients had elevated lactate dehydrogenase with a median of 570 u/L (245–2991) and a low haptoglobin median of 28 u/L (10–150). Thrombocytopenia was present in 18 (94.7%) cases with a median of 79 fl (22–180). Severe thrombocytopenia of ≤ 30 was identified in three (15.8%) cases. The majority (63.1%) of the patients presented with high blood pressure with moderate to severe AKI. Ten (52.6%) of those who presented with severe AKI required dialysis. Proteinuria and microscopic hematuria were present in 18 (94.7%) patients with a median of 387.0 mg/mmol (31.1–858.3). Nephrotic range proteinuria was reported in five (26.3%) patients. The complement activity assay for both C3 and C4 was reported in 18 (94.7%) patients. Six (31.6%) patients had low C3 levels with a median value of 927 mg/L (113–1370), and C4 activity with a median of 226.5 mg/L (150.0–423.0). Upon follow-up, persistently low C3 level was found in only 20.0% of patients.

Classical pathway activities were performed in 11 (57.9%) cases and were in the range of 34–115% (reference range = 65–135%). Classical pathway dysregulation was reported in 11.0% of cases. Alternative pathway dysregulation was found in four (21.1%) cases with values in the range of 10–128%. Among patients with normal alternative

Table 3: The median of the laboratory parameters of Omani patients with atypical hemolytic uremic syndrome at the time of presentation and at three months follow-up (N = 19).

Parameter	At presentation		At three months follow-up	
	Median	Range	Median	Range
Bilirubin, umol/L	17	4–78	7	4–27
ALT, U/L	18	5–253	12	5–189
ALP, U/L	78	42–588	80	45–269
Albumin, g/L	31	20–40	39	26–50
C-reactive protein, mg/L	29.1	2.3–94.2	9	0.4–20.0
Urea, mmol/L	28.8	4.2–49.9	7.1	2.3–16.0
Creatinine, umol/L	358	45–1040	121	35–862
Urine PCR	387.0	31.1–8583.3	44.5	12.8–582
eGFR, mL/min/1.73	10	2–37	41	4–100
Hemoglobin, g/dL	8.0	4.1–10.9	11.6	7.3–13.7
Total leucocytic count	7.6	4.5–14.8	5.8	2.4–12.8
Platelet, 10^9/L	79	22–180	237	64–346
Haptoglobin, u/L	28	10–150	1230	390–2300
Lactate dehydrogenase, u/L	570	245–2991	208	141–379
Prothrombin time, sec	11.1	9.6–16.4	11.1	10.2–17.4
Partial thromboplastin time, sec	33.8	25.8–48.0	35.5	30.2–46
Thrombin time, sec	17.8	13.4–22.4	16.1	11.6–20.8
Fibrinogen, g/L	2.6	0.8–4.8	2.8	1.4–7.0
C3, mg/L	927	113–1370	960	240–1784
C4, mg/L	226.5	150.0–423.0	280	170–549

Results are expressed as numerical values, and medians (range) for continuous variables, unless otherwise indicated.
ALT: alanine aminotransferase; ALP: alkaline phosphatase; PCR: polymerase chain reaction; eGFR: estimated glomerular filtration rate; C3: complement component 3; C4: complement component 4.

pathway activity, one was already being treated with eculizumab. The test for C5b-9 membrane attack complex activity was performed in 14 (73.7%) patients, six of whom had elevated levels. Low complement factor H protein activity was found in six (31.6%) cases (120–500 ug/mL; normal: 284–528). Anti-factor H autoantibodies were found in five (26.3%) cases, range = 3–420 u/mL (normal: < 60). ADAMTS13 activity was normal in all cases.

Renal biopsy was performed in 14 (73.7%) cases for performing light microscopy, immunofluorescence, and electron microscopy. Ten biopsies were taken from native kidneys, of which nine were usable. Features of acute TMA were reported in five of the biopsied cases, a combination of chronic acute TMA in three, and chronic TMA in one. Three biopsies were taken from grafted kidneys, one of which showed a recurrence nearly one year post-transplant with mild acute TMA involving a few arterioles. There were no features to suggest rejection, and C4d was negative.

Of the 11 (57.9%) patients who underwent genetic testing, five (45.5%) had a known pathogenic variant in aHUS susceptibility genes, and four had variants of unknown significance (VUS). Homozygous full gene deletions for the susceptibility *CFHR1* and *CFHR3* genes were identified in patients 1 and 6, whereas patient 2 was heterozygous for this deletion mutation, making its role in the development of the HUS uncertain. Patient 4 carried a homozygous missense variant of unknown significance in the *CFHR3* gene (c.209T>C). Patient 3 probably had PIGA-related normal pressure hydrocephalus with aplastic anemia related to a somatic duplication in the *PIGA* gene. Patients 5 and 8 were heterozygous for pathogenic variants in the *CD46* (c.175C>T, p.Arg59*) and *CHF* (p.Arg1206Cys) genes, respectively. Other identified VUSs included the CFH heterozygous intronic variant (c.965-6T>C) with an unknown splicing effect (patient 5), as well as the CFHR5 heterozygous variant (c.1561T>A and p.Leu521Ile) (patient 6), THBD heterozygous variant (c.131C>T and p.Thr44IIe) (patient 7), and heterozygous variants in *C3* (c.2901C >T and p.Leu967Leu) and *CFH* (c.3677C>A. p.Pro122Gln) genes (patient 9) [Table 4].

Table 5 shows the pattern of treatment and the associated renal outcome and mortality at the three-month follow-up, then at the last follow-up, which had a median of five (1–7) years. Plasma exchange followed by eculizumab was the treatment strategy in 11 (57.9%). Complete renal remission was attained by seven (36.4%) patients while the remaining 12 continued to be dialysis dependent. Three patients underwent kidney transplants. Plasma

Table 4: The genetic analysis of Omani patients with atypical hemolytic uremic syndrome (aHUS) (n = 9).

Patient No.	Gene involved	Gene variant	Zygosity	Inheritance	Variant classification and predicted role in aHUS phenotype
1	*CFHR1*, *CFHR3*	1q31.1del	Homozygous	AD/AR	Pathogenic, susceptibility alleles in the homozygous state.
2	*CFHR1*, *CFHR3*	1q31.1del	Heterozygous	AD/AR	Pathogenic, susceptibility allele, uncertain increase in risk in the heterozygous state.
3	*PIGA*	Whole gene duplication†	Hemizygous	Sporadic somatic mutations	Probably a somatic mutation that also explains the aplastic anemia identified in this patient.
4	*CFHR3*	c.209T>C, p.IIe70Thr	Homozygous	AD/AR	VUS
5	*CD46* *CFH*	c.175C>T, p.Arg59* c.965-6T>C	Heterozygous Heterozygous	AD/AR AD/AR	Pathogenic, susceptibility allele. VUS
6	*CFHR1*, *CFHR3*, *CFHR5*	1q31.1del c.1561T>A, p.Leu521Ile	Homozygous Heterozygous	AD/AR AD	Pathogenic, susceptibility allele in the homozygous state. VUS
7	*THBD*	c.131C >T, p.Thr44IIe	Heterozygous	AD	VUS
8	*CFH*	p.Arg1206Cys	Heterozygous	AD/AR	Pathogenic, susceptibility allele.
9	*C3*, *CFH*	c.2901C >T, p.Leu967Leu c.3677C>A. p.Pro122Gln	Heterozygous Heterozygous	AD AD/AR	VUS VUS

This table excludes two patients whose results were negative. AD: autosomal dominant; AR: autosomal recessive; VUS: variant of uncertain significance. †Duplication segment appears to be larger and involves several genes on chromosome X, but array comparative genomic hybridization was not done to define the exact size.

Table 5: The treatments and the associated renal outcome (or mortality) among Omani patients with atypical hemolytic uremic syndrome (N = 19).

Treatment options	Total patients n (%)	Initial outcomes (three months)				Last follow-up outcomes Median 5 (1–7) years		
		Renal remission n (%)	CKD n (%)	ESRD/ dialysis n (%)	Death n (%)	Renal remission n (%)	ESRD/ dialysis n (%)	Death n (%)
Conservative treatment	3 (15.8)	0 (0.0)	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	2 (66.7)	1 (33.3)
PE/PI	2 (10.5)	2 (100)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)	0 (0.0)	0 (0.0)
PE and eculizumab	11 (57.9)	4 (36.4)	0 (0.0)	7 (63.6)	1 (9.1)	0 (0.0)	10† (100)	2 (20.0)
Eculizumab	3 (15.8)	3 (100)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100)	0 (0.0)	0 (0.0)

Results are expressed as numerical values and percentages for categorical variables unless otherwise indicated.
CKD: chronic kidney disease; ESRD: end-stage renal disease (requiring renal replacement therapy); PE: plasma exchange; PI: plasma infusion
†Three patients went for kidney transplants. Plasma exchange was given for 5–10 sessions and if the response failed, eculizumab was initiated (except for children).
See Table 3 for the three-month follow-up response.

exchange alone was the treatment for one patient, and plasma infusion was the treatment choice for another; the remaining three patients were managed conservatively. Three pediatric patients received eculizumab as first-line therapy. All three had complete hematological recovery and renal remission at the three-month follow-up, which they sustained at the last follow-up as well. Overall, there were four (21.1%) deaths, all attributable to the disease process.

DISCUSSION

This is the first report of the clinical presentation and genetic results of adult and pediatric patients diagnosed with aHUS in Oman. Though the Omani population is known to have a high rate of consanguinity, this study failed to find a familial trend in the diagnosed cases.[19]

Some of our patients presented with peculiar unreported clinical manifestations, which imposed significant diagnostic and management challenges. Three patients had optic atrophy. This ocular manifestation is increasingly found in the literature but only as case reports.[20,21] One of our female patients had cardiac involvement and continued to have volume overload and pulmonary edema. Her echocardiogram showed severe mitral regurgitation. This could stem from ischemia of chordae tendineae. A male patient had conjunctival hemorrhage. As his platelet level was 22 10^9/L, he was initially evaluated for possible hemorrhagic fever and his serology for rickettsia was positive. As aHUS is usually a thrombotic disease, his conjunctival hemorrhage could be attributed to thrombocytopenia or severe hypertension. Another patient who presented with clinical features of liver cirrhosis with portal vein thrombosis had to be managed conservatively due to diagnostic challenges.

In this cohort, complement activation and functional assay did not have a diagnostic value. However, low C3 levels were found in 31.6% of patients at presentation. This is similar to the findings of other studies, which have reported even more low-C3 incidence among patients with C3 or CFB mutations.[8,10,14,21] Four of our patients who developed acute TMA post-kidney transplant had neither undergone native kidney biopsies nor investigated for donor-specific antibodies. The diagnostic challenge was the differentiation of the TMA from antibody-mediated rejection. Furthermore, two of these four patients had C4d positivity. Although only 11 of 19 patients in the current cohort underwent molecular genetic testing, the yield was relatively high. The most frequent pathogenic variant was in *CFH* gene, similar to the prevalence found among Caucasian populations.[22–24]

The identification of *CFHR1* and *CFHR3* gene deletions in the homozygous state further confirms their role in the pathogenesis of aHUS.[25] However, molecular genetic testing of the cases in this study had been conducted over 12 years, at different laboratories that used different methodologies, which made the comparison of results not possible.

Another issue was the segregation analysis was not performed to assess the pathogenicity of VUS. Given the severity of aHUS in six of our patients

with VUS, establishing the pathogenic relevance of these variants was of clinical importance. Five out of the six VUS were in *CFH* and all the six were in *C3*. A higher frequency of the *C3* variant was reported in an Asian population.[26] In this study, complete renal remission on the last follow-up was achieved in 50.0% of the patients who received eculizumab. This rate is similar to what was reported by Fakhouri et al.[27]

All seven patients who did not respond to eculizumab were adults with clinical evidence of chronic disease, two of whom had TMA in their renal grafts. Three of these seven patients passed away (patients no. 1, 2, and 8 in Table 4). Patients 1 and 2 had combined pathogenic mutation in *CFH* gene and factor H autoantibodies. Patient 1, a female, had a very aggressive disease course with extra-renal thrombosis, early recurrence of aHUS after kidney transplant and graft failure. On dialysis, she developed calcific uremic arteriolopathy and died five years after the diagnosis of aHUS. Patient 2 died after a massive ischemic stroke in the year of diagnosis. Patient 8 (adult male) was diagnosed with aHUS after kidney transplant and died following a stroke three months post-transplantation.

Eculizumab is reported to be effective against aHUS if initiated early.[11,21,28,29] Persistence of hemolysis or lack of improvement in renal function after 3–5 daily plasma exchanges is a criterion for uncontrolled TMA and is an indication for initiating eculizumab.[30] There are limited reports of eculizumab being used as the first-line therapy of *de novo* aHUS in native kidneys. Ohanian et al,[31] reported the successful use of eculizumab as first-line therapy in a severe case of aHUS complicated by central nervous system involvement. In an open-label single-arm phase 2 trial, Fakhouri et al,[29] reported discontinuation of dialysis in 79% of patients treated with eculizumab as first-line treatment.[30] In the current cohort, eculizumab as first-line therapy in three cases of aHUS resulted in full recovery. The use of eculizumab as a treatment for secondary HUS is not yet established.[26] One of our patients was positive for rickettsia, and despite treatment with doxycycline and plasmapheresis, he had a worsening course of aHUS and required intubation and intensive care unit care. After the first dose of eculizumab, dialysis was stopped and he was extubated. Genetic testing for compliments yielded negative results. Despite eculizumab's lifesaving qualities, it remains out of the reach of most patients due to its prohibitive cost.

Rickettsia infection is known to cause AKI and is associated with poor renal outcomes.[32] Postmortem examination of such patients has revealed features of TMA.[32] Three of our patients received conservative treatment because they presented with established CKD and no features of active aHUS. One of them died three years after the diagnosis due to a stroke. Screening of recurrent aHUS post-kidney transplant and after initiation of dialysis is essential particularly if treatment with eculizumab is discontinued. Stroke is a serious vascular manifestation of aHUS that occurs suddenly and is hard to predict.[12] Hence, for patients with aHUS who manifested with stroke or another serious cerebrovascular event one could make a case for a prolonged course of eculizumab treatment.

This study has the typical limitations of most retrospective studies. First, because the molecular genetic investigations of the participants had been conducted over 12 years, that too in different laboratories using different methodologies, their results could not be compared. Second, segregation analysis was not performed to assess the pathogenicity of VUSs. Third, this study documents only patients who sought tertiary care, potentially excluding many undiagnosed aHUS cases in the population.

CONCLUSION

The aHUS in Oman is a multiple-hit disorder, similar to reports elsewhere. The wide spectrum and multiple faces of presentation render this disease a significant diagnostic challenge, often delaying treatment. The identification of *CFH1* and *CFHR3* gene deletions in a homozygous state further confirms their role in the pathogenesis of aHUS. The VUSs were associated with aggressive disease and were likely to be pathogenic. Eculizumab is the key to suppressing complement activation, and where affordable, should be the first-line therapy and delivered as early as possible.

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