Review Article

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Spur Cell Anaemia in Cirrhosis: A Narrative Review

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The presence of anaemia has been linked to increased complications and a worse prognosis in cirrhosis. Spur cell anaemia (SCA) is a specific form of haemolytic anaemia reported in patients with advanced cirrhosis. The literature on the entity has not been systematically reviewed, despite the classical association and frequent association with worse outcomes. We undertook a narrative review of available literature on SCA which yielded only 4 were original studies, one case series and the rest of the literature as case reports and clinical images. SCA is usually defined by the presence of spur cell rate of ≥5%, although there remains a lack of consensus in the definition. SCA has been classically associated with alcohol-related cirrhosis but can be seen across the spectrum of cirrhosis and acute to chronic liver failure. Patients with SCA tend to have evidence of higher grades of liver dysfunction, abnormal lipid profiles, worse prognostic scores and a high mortality. Experimental therapies including corticosteroids, pentoxifylline, flunarizine and plasmapheresis has been tried with variable effect, but liver transplantation remains the management of choice. We propose a stepwise approach to diagnosis and re-enforce the need for further prospective research, especially in subgroups of advanced cirrhosis like acute to chronic liver failure. (J Clin Exp Hepatol xxxx;xxx:xxx)

Anaemia is a commonly encountered complication in patients with chronic liver disease and cirrhosis and is seen in 53–66% of the patients.[1,2] There are diverse aetiologies for anaemia in cirrhosis and frequently multiple causes co-exist.[2] The presence of anaemia has been linked to increased complications and a worse prognosis in cirrhosis.[2,3] Spur cell anaemia (SCA) is a specific form of haemolytic anaemia reported in patients with advanced cirrhosis and has been associated with grave outcomes.[4] The entity was initially reported in a seminal paper by Smith *et al.*, noting bizarre erythrocytes with "curious projections" on their surfaces in a young male with alcohol-related cirrhosis and haemolytic anaemia.[5] However, the literature on the entity has not been systematically reviewed, despite the classical association and frequent association with worse outcomes. We undertook a narrative review of available literature on SCA in cirrhosis in this background.

METHODS

We conducted this narrative review according to guidelines and checklist provided by Green *et al.*[6] (Supplementary Table 1). Literature for this review was identified using specific search terms as Boolean combinations in MEDLINE and EMBASE (Supplementary Table 2). All studies from the inception of the particular database to 26th January 2022 were searched. We reviewed all designs of articles (cohort studies, case–control studies, case series, case reports). Articles published only as conference abstracts were excluded and language was restricted to English.

RESULTS

We identified 175 total articles in accordance to the prespecified search strategy. Out of these, only 4 were original studies[7–10] and one case series.[11] The rest of the literature on SCA in cirrhosis was as case reports and clinical images. In the following sections, we comprehensively reviewed the available literature.

Nomenclature and Definition of Spur Cells and Spur Cell Anaemia

Spur cells, also known as acanthocytes (Greek acantha: thorn), are characteristic red blood cells that have spicules or spike-like projections on the surface, with the projections being irregular (in width and length) and unevenly distributed.[12] These cells need to be differentiated from a similar type of cells known as burr cells (echinocytes) in whom the spike-like

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Abbreviations: ACLF: Acute on chronic liver failure; CTP: Child Turcotte Pugh; HCV: Hepatitis C Virus; HDL: High density lipoprotein; HEV: Hepatitis E Virus; INR: International Normalisation Ratio; LDH: Lactate Dehydrogenase; LDL: Low density lipoprotein; MELD: Model for end stage liver disease; NASH: Non-alcoholic steatohepatitis; OLT: Orthotopic liver transplantation; SCA: Spur cell anaemia; SMT: Standard medical Therapy; TC: Total Cholesterol; TG: Triglycerides; VLDL: Vey low density lipoprotein
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Table 1 Summary of Studies Describing Spur Cell Anaemia.

Authors/Year/ Country	Design/ Direction	Number of patients	Study population and selection criteria	Demographic characteristics	Haematological parameters	Liver function parameters	Lipid profile	Prognostic scores	Key findings	Mortality in SCA
Alexopoulou *et al.*/2014/ Greece	Cohort/ Prospective	Total: 116 With SCA: 36 Without SCA: 80	Decompensated cirrhosis **Exclusion:** Renal failure, sepsis, acute alcoholic hepatitis, bleeding, other haemolytic anaemia	Age: 55 (49–65.5) Males: 89%	Haemoglobin (g/dl) 8.9 (8.5–10.3) Reticulocyte (%): 4 (2.5–6)	Bilirubin (mg/dl): 9.5 (5.2–14.2) Albumin: 3.2 (2.8–3.5) INR: 1.8 (1.6–2.3)	TC (mg/dl): 99 (82–126) TG (mg/dl): 81 (50–110) LDL (mg/dl): 75 (64–92) HDL (mg/dl): 11 (7–23) VLDL (mg/dl): 16 (10–23)	MELD: 21.5 (15–25.5)	Advanced disease (Higher MELD) and worse survival. SCA is an independent predictor for mortality (3.17 [95% CI 1.55–6.48]).	1 month survival: 77% 3-month survival: 33%
Vassiliadis *et al.*/2010/ Greece	Cohort/ Prospective Median follow-up: 150 days	Total: 54 No spur cells: 28 1–4% spur cells: 17 ≥5% spur cells: 9	Advanced cirrhosis (CTP ≥ 7) Exclusion: HCC, Chronic renal failure, haemoglobinopathies, Coombs positive anaemia, sepsis, active bleeding, cholestatic liver disease, anticoagulant therapy	Age: 50 (44–76) Males: Males 88.9%	Haemoglobin (g/dl) 8.1 (7.1–10.5) Reticulocyte (%): 4.5 (2.3–4.8)	Bilirubin (mg/dl): 14.7 (2.5–30.1) Indirect: 3.8 (0.5–20.7) INR: 2.3 (2.0–4.7)	TC (mg/dl): 84 (49–102) Triglycerides (mg/dl): 88 (58–102) LDL (mg/dl): 39 (14–60) HDL (mg/dl): 25 (18–30) VLDL (mg/dl): NA	MELD: 30 (20–40) CTP score: 12 (10–13)	Patients with SCA: Higher MELD Low TC, TG and LDL	3-month survival: No spur cell: 92.3% 1–4% Spur cells: 81.3% ≥5% spur cells: 22% 1-year survival: Similar
Pascoe *et al.*/ 1999/ Australia	Cross sectional	Total: 36	Patents with Alcoholic liver disease undergoing OLT Exclusion: Acute alcoholic hepatitis	Age 39 (32–66) Males: 82%	NA	NA	NA	NA	7/36 (19.4%) had SCA	–
Virk *et al.*/2021/ USA	Multicentric cohort study	69 patients with SCA	Decompensated cirrhosis Exclusion: Presence of alternative causes of haemolysis,	Age: 53 (42.2–59.4) Males: 53.6%	Haemoglobin (g/dl) 7 (6.5–7.7) Reticulocyte (%): 6 (4.1–7.9)	Bilirubin (mg/dl): 13 (8.6–19.2) Indirect: 8 (5.1–11) INR: 2 (1.8–2.8) Albumin: 3 3 (2.5–3.3)	NA	MELD: 30 (25.8–34) CTP score: 11 (10–12)	56.5% were transfusion dependent All patients (n = 11) who underwent LT has reversal of SCA with post LT 3 month survival of 81.8%	57 patients who did not undergo LT had a 3 month mortality of 94.8%

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Table 1 (*Continued*)

Authors/Year/Country	Design/Direction	Number of patients	Study population and selection criteria	Demographic characteristics	Haematological parameters	Liver function parameters	Lipid profile	Prognostic scores	Key findings	Mortality in SCA
Kedarisetty *et al.*/2020/India	Case series	5 patients with SCA	Included patients with Acute on chronic liver failure	Age 38.6 (31–49) All males	–	–	–	–	All patients had alcohol as the cause of chronicity while 2 patients had HEV as an acute insult and 3 were due alcoholic hepatitis.	Outcomes were known in 4 patients of whom 3 (75%) died

ACLF: Acute on chronic liver failure; CTP: Child Turcotte Pugh; MELD: Model for end stage liver disease; NASH: Non alcoholic steatohepatitis; HCV: Hepatitis C Virus; TC: Total Cholesterol; TG: Triglycerides; INR: International Normalisation Ratio; LDL: Low density lipoprotein; LDH: Lactate Dehydrogenase; HDL: High density lipoprotein; SMT: Standard medical Therapy; VLDL: Very low density lipoprotein; OLT: Orthotopic liver transplantation; HEV: Hepatitis E Virus; SCA: Spur cell anaemia; NA: Not available; LT: Liver Transplantation.

projections are regular and evenly distributed.[13] These cells have been described in multiple conditions like abetalipoproteinemia, hypothyroidism, neuroaconthocytosis, abnormalities of Kell blood group system (McLeod phenotype), myelodysplasia, anorexia nervosa, patients undergoing splenectomy and have also been reported with certain drugs like statins and misoprostol.[14–16] Although the terms spur cells and acanthocytes are usually used interchangeably, some authors prefer to reserve the term acanthocytes specifically for abetalipoproteinemia.[17] Additionally, erythrocytes simulating spur cells with a spiculated appearance can also be seen due to an ethylene diamine tetra-acetic acid artefact after a delay of more than 6 h between storage and smear preparation.[18] In the context of liver disease, spur cells have been classically described in haemolytic anaemias seen in cirrhosis, especially with alcohol-related cirrhosis.[4] Traditionally, SCA has been defined as those having a spur cell rate of ≥5% in the presence of associated features of haemolysis.[7,8] However, there remains a lack of consensus on the exact definition of SCA.[10]

Proposed Mechanisms for SCA

Since the earliest descriptions of SCA in cirrhosis in the 1960s, observations and hypotheses were made that a protein or protein-bound substance was responsible for inducing the morphological changes in erythrocytes in SCA. These observations primarily stemmed from the fact that when normal erythrocytes were mixed and incubated with serum of patients suspected of SCA, similar changes were induced in the normal erythrocytes.[5] In a seminal report, Martinez-Maldonado demonstrated the role of low density lipoproteins in the alteration of erythrocytes' shape (spur-formation), thereby making them susceptible to accelerated haemolysis.[19] In further works directed at identifying the mechanism, Cooper *et al.* demonstrated the alteration in cholesterol to phospholipid ratio in red cell membranes with free cholesterol being the predominant component.[20] While looking at specific lipoprotein abnormalities in alcohol-related cirrhosis, Duhamel *et al.* demonstrated significantly lower Apo-AII, high density lipoprotein 3 and low density lipoprotein levels and proposed the central role of Apo-AII deficiency in altering membrane morphology and susceptibility to haemolysis.[17] To further deliberate on the mechanistic aspects, the authors suggested decreased synthetic capacities of nascent lipoproteins and lipolytic enzymes (Lecithin Cholesterol Acyl-Transferase (LCAT), lipase) in cirrhosis compounded by deficient secretory capacities due to dietary deficiencies in alcoholics.[17] Overall, the abnormal red cell morphology with alterations in the red cell membrane eventually lead to markedly reduced survival and combined with hypersplenism in advanced cirrhosis proposed forms the mechanistic basis of excessive haemolysis observed in SCA.

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Table 2 Summary of Case Reports on SCA.

Author, Year	Age, Sex	Aetiology of cirrhosis	Haematological parameters	Liver function tests	Lipid profile	Prognostic scores	Therapy	Outcome
Martin *et al.* 2004[21]	48, Male	Cryptogenic	Haemoglobin (g/dl) 7.7 Reticulocyte (%): 4 (2.5–6) LDH (mg/dl) 1291 Haptoglobin (0.072 g/l) 0.072 Coombs test: Negative	Bilirubin (mg/dl): 23 (Indirect: 15 mg/dl) Albumin: 2.2 INR: NA PTI: 25%	–	–	Standard medical therapy	Death
Haruta *et al.* 2007[22]	61, Male	NASH	Haemoglobin (g/dl) 5.2 Reticulocyte (%): 9.1 LDH (mg/dl) 331 Haptoglobin (mg/dl) < 12 Iron (mg/dl) 155 Ferritin (ng/ml) 590 Coombs Test: Negative	Bilirubin (mg/dl): 13.6 (Indirect: 9.6 mg/dl) Albumin: 2.3 INR: NA PTI: 25.4%	TC (mg/dl): 135 Triglycerides (mg/dl): 48 LDL (mg/dl): NA HDL): 29 VLDL (mg/dl): NA	–	SMT	Death
Goel *et al.* 2008[23]	47, male	Alcohol	Haemoglobin (g/dl) 7.3 Reticulocyte (%): Na LDH (u/L): 588 Coombs Test: Negative	Bilirubin (mg/dl): 11 Albumin: 3.1 INR: NA PTI: 22.8%	–	–	SMT	Transplant waitlist
Karam *et al.* 2018[24]	66, male	NASH	Haemoglobin (g/dl) 6.6 Reticulocyte (%): 5.2 LDH (u/L): 1104 Haptoglobulin (mg/dl) < 7.75 Coombs Test: Negative	Bilirubin (mg/dl): 11.2 (Indirect: 5.7 mg/dl) Albumin: NA INR: 1.5	–	CTP: 10	SMT plus steroids (methylprednisolone × 7 days)	Improved

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Table 2 (*Continued*)

Author, Year	Age, Sex	Aetiology of cirrhosis	Haematological parameters	Liver function tests	Lipid profile	Prognostic scores	Therapy	Outcome
Miki *et al.*[25]	52, male	Alcohol	Haemoglobin (g/dl) 7.9 Reticulocyte (%): 22.4 LDH (u/L): 438 Haptoglobulin (mg/dl) 3 Coombs Test: Negative Spur cells: 25%	Bilirubin (mg/dl): 15.6 (Indirect: 7.6 mg/dl) Albumin: 2.3 INR: 1.65	TC (mg/dl): 121 Triglycerides (mg/dl): 53 LDL (mg/dl): 29 HDL): 15 VLDL (mg/dl): NA	CTP: 12	SMT plus plasmapharesis	Improved
Miwa *et al.* 2018[26]	26	Alcohol	Haemoglobin (g/dl) 2.1 Reticulocyte (%): 5 LDH (u/L): 449 Haptoglobulin (mg/dl) < 10	Bilirubin (mg/dl): 12.7 (Indirect: 7.36 mg/dl) Albumin: 3 INR: 2.1 PTI : 30%	TC (mg/dl): 215 Triglycerides (mg/dl): 83 LDL (mg/dl): 56 HDL): 39 VLDL (mg/dl): NA	CTP 11 MELD 24	SMT (Blood transfusion)	Improved
Privitera *et al.* 2016[12]	44, male	Alcohol	Haemoglobin (g/dl) 7.4 Reticulocyte (%): NA LDH (u/L): 581 Haptoglobulin (mg/dl) 2 Coombs Test: Negative	Bilirubin (mg/dl): 18.2 (Indirect: 11.26 mg/dl) Albumin: 2.8 INR: 2.5	TC (mg/dl): 124 Triglycerides (mg/dl): 45 LDL (mg/dl): 94 HDL): 21 HDL_3 0.23	CTP 11	SMT	Transplant waitlist
Raffa *et al.* 2021[27]	57, male	Alcohol	Haemoglobin (g/dl) 7.4 Reticulocyte (%): 16% LDH (u/L): 263 Haptoglobulin (mg/dl) < 10 Coombs Test: Negative	Bilirubin (mg/dl): 15.4 (Indirect: 9.26 mg/dl) Albumin: 2.3 INR: 2.7	TC (mg/dl): 132 Triglycerides (mg/dl): 74 LDL (mg/dl): 59 HDL): 59	MELD 30 CTP C	SMT plus corticosteroids plus IVIg	Death

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Table 2 (*Continued*)

Author, Year	Age, Sex	Aetiology of cirrhosis	Haematological parameters	Liver function tests	Lipid profile	Prognostic scores	Therapy	Outcome
Shah *et al.* 2014[28]	32, male	Alcohol + HCV	Haemoglobin (g/dl) 6.2 Reticulocyte (%): NA LDH (u/L): 390 (mg/dl) Undetectable Coombs Test: NA	Bilirubin (mg/dl): 27 (Indirect: 14 mg/dl) Albumin: 2.3 INR: 3.3	TC (mg/dl): 97 Triglycerides (mg/dl): 61 LDL (mg/dl): 34 HDL): 51 VLDL (mg/dl): 12	–	SMT	Transplant waitlist
Zimmer *et al.* 2014[29]	60, male	Alcohol	Haemoglobin (g/dl) 6.1 Reticulocyte (%): 5.5% LDH (u/L): 836 Haptoglobulin (mg/dl) Undetectable Coombs Test: Negative	Bilirubin (mg/dl): 27 (Indirect: 17 mg/dl) Albumin: 2.3 INR: 3.3	–	CTP C	SMT	Death
Sangha *et al.* 2020[31]	45, female	Alcohol	Haemoglobin (g/dl) 4.3 Reticulocyte (%): 18.3% LDH (u/L): 851 Haptoglobulin (mg/dl) Undetectable Coombs Test: Negative	Bilirubin (mg/dl): 19.6 (Indirect: 9.2 mg/dl) INR: 2.5	–	CTP C MELD 30	SMT plus pentoxifylline	Death within 3 months
Sundaram *et al.* 2006[30]	43, female	Alcohol	Haemoglobin (g/dl) 11.2 Reticulocyte: 2×10^5/L LDH (u/L): NA Haptoglobulin (mg/dl) Undetectable Coombs Test: NA	Bilirubin (mg/dl): 30 (Indirect: 15.7 mg/dl) INR: 4.1	–	CTP C MELD 40	SMT	Death within 2 months
Aihara *et al.* 2001[32]	30, male	Alcohol	Haemoglobin (g/dl) 7.7 Reticulocyte: 152×10^5/L LDH (u/L): 342 Haptoglobulin (mg/dl) 60 Coombs Test: Negative	Bilirubin (mg/dl): 9.1 Albumin: NA INR: NA	TC (mg/dl): 386 Phospholipids 322	–	Flunarizine, pentoxifylline and cholestyramine	Improved

ACLF: Acute on chronic liver failure; CTP: Child Turcotte Pugh; MELD: Model for end stage liver disease; NASH: Non alcoholic steatohepatitis; HCV: Hepatitis C Virus; TC: Total Cholesterol; TG: Triglycerides; INR: International Normalisation Ratio; LDL: Low density lipoprotein; LDH: Lactate Dehydrogenase; HDL: High density lipoprotein; SMT: Standard medical Therapy; VLDL: Very low density lipoprotein; OLT: Orthotopic liver transplantation; HEV: Hepatitis E Virus; SCA: Spur cell anaemia; PTI: Prothrombin index; NA: Not available.

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Prevalence of SCA in Cirrhosis

The prevalence of SCA in patients with cirrhosis has been variably reported. Alexopoulou *et al.* in a study from Greece including 116 patients with cirrhosis, 36 patients (31.01%) had a spur cell rate of ≥5%.[8] Although SCA is commonly believed to be associated with alcohol-related cirrhosis, in this study, there was no difference based on alcohol versus other aetiologies (44% vs. 55%, $P = 0.2$).[8] Vassiliadis *et al.* in a study including 54 patients with advanced liver disease (Child Turcotte Pugh [CTP] ≥ 7), showed that spur cells were present at a rate of 1–4% in 17 (31.4%) and >5% in 9 (16.6%) patients.[7] The most common aetiology of cirrhosis in patients with a spur cell rate of ≥5% was alcohol combined with viruses.[7] Pascoe *et al.* reported spur cell anaemia in 7 (19.4%) of 36 patients with alcohol-related cirrhosis. However, the study did not explicitly clarify the definition of SCA and included any patient with haemoglobin <10 g/dl and significant acanthocytes on peripheral smear examination.[9]

Biochemical Characteristics and Prognostic Scores in Patients with SCA

Overall, SCA has been reported in patients with advanced liver disease in patients having decompensated cirrhosis or acute on chronic liver failure.[8,11] Patients with SCA tend to have evidence of higher grades of liver dysfunction, abnormal lipid profiles and worse prognostic scores (model for end stage liver disease [MELD], CTP). Key biochemical findings from major studies reporting SCA in cirrhosis is summarised in Table 1.

Outcomes of Patients with SCA

The presence of SCA in cirrhosis is associated with both advanced liver disease as well as an abysmal prognosis. The study by Alexopoulou *et al.* showed that in patients with spur cell rate ≥5%, the survival at 1-month and 3-month was 77% and 33%, respectively, with an overall median survival of 1.9 months.[8] SCA was shown to be an independent predictor of mortality in this group. Since at baseline, patients with SCA tend to have intrinsically more advanced liver disease, the authors adjusted the mortality for age, gender, MELD, sodium and liver function parameters and demonstrated those with spur cell rate of ≥5% had a three times higher risk for mortality than those with spur cells 0–4% (hazard ratio = 3.17 [95% confidence interval 1.55–6.48]).[8] Vassiliadis *et al.* reported a 3-month survival in patients without spur cells, with 1–4% spur cells and ≥5% spur cells as 92.3%, 81.3% and 22.2%, respectively, reinforcing the high mortality in patients with spur cells rate of ≥5%.[7] In the most recently reported cohort of 69 patients with SCA, 58 patients who did not undergo a transplant had an adverse outcome, while 11 patients who underwent transplantation had an immediate and complete resolution of SCA.[10] The authors noted that both the corresponding MELD-Na and CTP scores consistently underestimated 90-day mortality in patients with SCA. Patients with SCA and a MELD-Na score between 20 and 29 had a 2.4 times higher likelihood of mortality than that expected based on the MELD-Na score alone.[10] Most of the studies on SCA have not specifically focused on patients with acute on chronic liver failure. In the only reported case series of five patients with acute to chronic liver failure, 75% of the patients with known outcomes died.[11]

Review of Literature from Case Reports

As highlighted before, most of the literature on SCA is confined to case reports and clinical images. A descriptive analysis of case reports published on SCA has been provided in Table 2.[12,21–32] The key features that emanate out of the case reports include a preponderance of SCA in patients with advanced cirrhosis, with a majority having alcohol as an aetiology although other aetiologies also being reported. Outcomes without liver transplant tend to be poor, and few cases report favourable outcomes using corticosteroids, plasmapheresis, intravenous immunoglobulin, flunarizine and pentoxifylline.[24,25,32] While the mechanisms by which each of these agents acts in SCA is uncertain, few hypotheses have been proposed. Corticosteroids have been postulated to have interactions with phospholipids in red blood cell membrane especially leading to dimyristoyl phosphatidylcholine hydration which has a protective role against haemolysis.[24,33] For pentoxifylline, the possible mechanisms that have been proposed include an increase in cellular ATP and calcium chelation leading to overall membrane stability.[31,34] Flunarizine, a calcium channel blocker, has been proposed to improve the deformability of erythrocytes by lowering the intracellular Ca^{2+} concentration.[32] The first reports of two cases describing the use of flunarizine showed prompt improvement with the drug administration. The authors hypothesised that the cholesterol accumulation in the RBC membrane is not the cause of haemolysis *per se* but rather the alteration of the transmembrane Ca^{2+} gradient that precipitates the event.[34] Although the use of plasmapheresis for SCA was initially reported from Japan with unfavourable outcomes, a recent report demonstrated a successful outcome with plasmapheresis and standard therapy and demonstration of lipid profile changes with plasmapheresis.[25]

SCA and Liver Transplantation

While the overall outcomes with SCA have been shown to be poor, liver transplantation has been advocated as the only definitive management. Multiple case reports and a recent multicentric study show favourable outcomes with LT in SCA.[10,35,36] According to the study by Virk *et al.*, all

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eleven patients who underwent LT had an immediate and complete resolution of SCA, and with around 59.0 patient-years of post-transplant follow-up, no transplanted patient developed features of haemolysis.[10] Therefore, given the grave outcomes with SCA, liver transplant seems to be the definitive therapy for patients with SCA, while transplant-ineligible patients should be offered some form of an investigational therapy.

Towards a Systematic Approach to SCA

SCA is an important entity to consider in patients with cirrhosis presenting with anaemia. Although classically associated with alcohol-related cirrhosis, the entity has been described across the spectrum of cirrhosis and acute on chronic liver failure. While anaemia is multifactorial, the approach to it involves a stepwise approach. The approach centres around ruling out common causes like gastrointestinal bleed, nutritional deficiencies, haemoglobinopathies, bone marrow dysfunction and the entire spectrum of haemolysis including entities like auto-immune haemolytic anaemia which have an immune nature of haemolysis determined by direct anti-globulin test.[37,38] Additionally, alcohol-related cirrhosis is frequently associated with secondary iron overload by alterations in the homeostasis between hepcidin and transferrin receptor.[39] In similar lines, although there is no consensus guidelines on the diagnosis of SCA, the diagnosis entails a systematic approach of establishing the presence of haemolysis, ruling out other causes and documentation of spur cells >5% in peripheral smear by an pathologist or haematologist.[10] A rare but important entity that is often confused with SCA is Zieve syndrome. This condition is primarily seen in patients with alcoholic hepatitis and alcohol-related cirrhosis and is thought to occur as a result of alcohol-related toxicity to the red cell membrane.[40] It is marked by jaundice, haemolysis and transient hyperlipidemia but characteristically does not show the presence of any spur cells on the peripheral smear examination. Additionally, in contrast to the grave prognosis of SCA, Zieve syndrome has a better prognosis with resolution after alcohol cessation.[7,27] Interestingly, peripheral smear features simulating auto-immune haemolytic anaemia although with direct antiglobin test negativity has been reported in Zieve syndrome.[41]

SCA is a form of haemolytic anaemia seen in patients with cirrhosis characterised by a significant proportion of spur cells. The condition has been associated with a grave prognosis and is seen across the spectrum of advanced decompensated cirrhosis. Experimental therapies have been tried with variable results, but liver transplantation remains the definitive solution in the face of otherwise dismal outcomes. Further research on subgroups of advanced cirrhosis like acute to chronic liver failure is mandated. There remains a dearth of literature that needs to be addressed in the future with well-designed prospective studies.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Akash Roy: Conceptualisation, Writing - Original Draft, Writing - Review and Editing.

Gajanan Rodge: Conceptualisation, Writing-review and editing, Visualisation.

Mahesh K Goenka: Writing - Review and Editing.

CONFLICTS OF INTEREST

The authors have none to declare.

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REFERENCES

1. Paternostro R, Kapzan L, Mandorfer M, et al. Anemia and iron deficiency in compensated and decompensated cirrhosis: prevalence and impact on clinical outcomes. *J Gastroenterol Hepatol*. 2020;35:1619–1627. https://doi.org/10.1111/JGH.14988.
2. Scheiner B, Semmler G, Maurer F, et al. Prevalence of and risk factors for anaemia in patients with advanced chronic liver disease. *Liver Int*. 2020;40:194–204. https://doi.org/10.1111/LIV.14229.
3. Bothou C, Rüschenbaum S, Kubesch A, et al. Anemia and systemic inflammation rather than arterial circulatory dysfunction predict decompensation of liver cirrhosis. *J Clin Med*. 2020:1263. https://doi.org/10.3390/JCM9051263.
4. Keyserling K, Koprowski S. Spur-cell anemia. *N Engl J Med*. 2018;379:774.
5. Smith JA, Lonergan ET, Sterling K. Spur-cell anemia: hemolytic anemia with red cells resembling acanthocytes in alcoholic cirrhosis. *N Engl J Med*. 1964;271:396–398.
6. Green BN, Johnson CD, Adams A. Writing narrative literature reviews for peer-reviewed journals: secrets of the trade. *J Chiropr Med*. 2006;5:101. https://doi.org/10.1016/S0899-3467(07)60142-6.
7. Vassiliadis T, Mpoumponaris A, Vakalopoulou S, et al. Spur cells and spur cell anemia in hospitalized patients with advanced liver disease: incidence and correlation with disease severity and survival. *Hepatol Res*. 2010;40:161–170. https://doi.org/10.1111/J.1872-034X.2009.00590.X.
8. Alexopoulou A, Vasilieva L, Kanellopoulou T, Pouriki S, Soultati A, Dourakis SP. Presence of spur cells as a highly predictive factor of mortality in patients with cirrhosis. *J Gastroenterol Hepatol*. 2014;29:830–834. https://doi.org/10.1111/JGH.12473.
9. Pascoe A, Kerlin P, Steadman C, et al. Spur cell anaemia and hepatic iron stores in patients with alcoholic liver disease undergoing orthotopic liver transplantation. *Gut*. 1999;45:301–305. https://doi.org/10.1136/GUT.45.2.301.
10. Virk ZM, Patel AA, Leaf RK, Al-Samkari H. Predictors of mortality and outcomes of liver transplant in spur cell hemolytic anemia. *Am J Hematol*. 2021;96:1611–1620. https://doi.org/10.1002/AJH.26359.
11. kumar Kedarisetty C, Kumar R. Spur cells causing severe and transfusion-refractory anemia in patients with acute-on-chronic liver failure. *Cureus*. 2020;12 https://doi.org/10.7759/CUREUS.10568.

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12. Privitera G, Meli G. An unusual cause of anemia in cirrhosis: spur cell anemia, a case report with review of literature. *Gastroenterol Hepatol From Bed to Bench*. 2016;9:335. https://doi.org/10.22037/ghfbb.v0i0.880.
13. Foglia A. The acanthocyte-echinocyte differential. *Swiss Med Wkly*. 2010 27;140 https://doi.org/10.4414/SMW.2010.13039.
14. Isa HM, Mohamed AM. Abetalipoproteinemia: three case reports, a novel microsomal triglyceride transfer protein gene mutation and a literature review. *J Clin Case Reports*. 2016;6 https://doi.org/10.4172/2165-7920.1000875.
15. De Franceschi L, Bosman GJCGM, Mohandas N. Abnormal red cell features associated with hereditary neurodegenerative disorders: the neuroacanthocytosis syndromes. *Curr Opin Hematol*. 2014;21:201–209. https://doi.org/10.1097/MOH.0000000000000035.
16. Filippini A, Villa G, Corrocher R, De Franceschi L. Acute hemolytic anemia with acanthocytosis associated with high-dose misoprostol for medical abortion. *Ann Emerg Med*. 2007;50:289–291. https://doi.org/10.1016/J.ANNEMERGMED.2006.09.001.
17. Duhamel G, Forgez P, Nalpas B, Berthelot P, Chapman MJ. Spur cells in patients with alcoholic liver cirrhosis are associated with reduced plasma levels of apoA-II, HDL3, and LDL. *J Lipid Res*. 1983;24:1612–1625. https://doi.org/10.1016/S0022-2275(20)37860-3.
18. Tyrrell L, Rose G, Shukri A, Kahwash SB. Morphologic changes in red blood cells: an illustrated review of clinically important light microscopic findings. *Malays J Pathol*. 2021;43:219–239.
19. Martinez-Maldonado M. Role of lipoproteins in the formation of spur cell anaemia. *J Clin Pathol*. 1968;21:620. https://doi.org/10.1136/JCP.21.5.620.
20. Cooper RA, Diloy Puray M, Lando P, Greenverg MS. An analysis of lipoproteins, bile acids, and red cell membranes associated with target cells and spur cells in patients with liver disease. *J Clin Invest*. 1972;51:3182–3192. https://doi.org/10.1172/JCI107145.
21. Martín M, De D, Heras L. Spur-cell anaemia in a patient with cirrhosis. Images in Hepatology. n.d. https://doi.org/10.1016/j.jhep.2004.01.025.
22. Haruta I, Hashimoto E, Kabutake A, Taniai M, Tokushige K, Shiratori K. Spur cell anemia associated with a cirrhotic nonalcoholic steatohepatitis patient. *Hepatol Res*. 2007;37:482–485. https://doi.org/10.1111/J.1872-034X.2007.00037.X.
23. Goel A, Kumar JDI, Nair SC, Joseph AJ, Viswabandya A, Eapen CE. Spur cell anemia associated with alcoholic cirrhosis. *J Gastroenterol Hepatol*. 2008;23:1463. https://doi.org/10.1111/J.1440-1746.2008.05589.X.
24. Karam D, Swiatkowski S, Purohit P, Agrawal B. Case Report: High-dose steroids as a therapeutic option in the management of spur cell haemolytic anaemia. *BMJ Case Rep*. 2018;2018 https://doi.org/10.1136/BCR-2017-223281.
25. Miki K, Maruki T, Imashuku S. Plasmapheresis for spur cell anemia in a patient with alcoholic liver cirrhosis. *Case Rep Hematol*. 2018;2018:1–4. https://doi.org/10.1155/2018/9513946.
26. Miwa T, Hatano Y, Kochi T, et al. Spur cell anemia related to alcoholic liver cirrhosis managed without liver transplantation: a case report and literature review. *Clin J Gastroenterol*. 2020;13:882–890. https://doi.org/10.1007/S12328-020-01142-3/FIGURES/6.
27. Raffa GA, Byrnes DM, Byrnes JJ. The diagnosis is in the smear: a case and review of spur cell anemia in cirrhosis. *Case Rep Hematol*. 2021;2021:1–5. https://doi.org/10.1155/2021/8883335.
28. Shah R, Patel A, John S. Spur cell anemia in end-stage liver disease: a zebra. *Am J Emerg Med*. 2014;32:944.e3–944.e4. https://doi.org/10.1016/J.AJEM.2014.01.027.
29. Zimmer V, Bittenbring J, Fries P, Lammert F. Severe mixed-type iron overload in alcoholic cirrhosis related to advanced spur cell anemia. *Ann Hepatol*. 2014;13:396–398. https://doi.org/10.1016/S1665-2681(19)30871-3.
30. Sundaram V, Al-Osaimi AMS, Lewis JJ, Lisman T, Caldwell SH. Severe prolongation of the INR in spur cell anemia of cirrhosis: true-true and related? *Dig Dis Sci*. 2006;51:1203–1205. https://doi.org/10.1007/S10620-006-8033-8.
31. Singh Sangha M, Aggarwal A, Sandhu J. Rare cause of non-immune hemolytic anemia in end-stage liver disease. n.d. *Case Rep Intern Med*. 2020 https://doi.org/10.5430/crim.v7n2p7
32. Aihara KI, Azuma H, Ikeda Y, et al. Successful combination therapy–flunarizine, pentoxifylline, and cholestyramine–for spur cell anemia. *Int J Hematol*. 2001;73:351–355. https://doi.org/10.1007/BF02981961.
33. Manrique-Moreno M, Londoño-Londoño J, Jemioła-Rzemińska M, et al. Structural effects of the Solanum steroids solasodine, diosgenin and solanine on human erythrocytes and molecular models of eukaryotic membranes. *Biochim Biophys Acta Biomembr*. 2014;1838:266–277. https://doi.org/10.1016/J.BBAMEM.2013.08.003.
34. Fossaluzza V, Rossi P. Flunarizine treatment for spur cell anaemia. *Br J Haematol*. 1983;55:715–717. https://doi.org/10.1111/J.1365-2141.1983.TB02857.X.
35. Kerlin P, Thomson A, Clouston A, Cobcroft R. Spur cell anaemia resolves after orthotopic liver transplantation (OLT). *Aust N Z J Med*. 1997;27:198–199. https://doi.org/10.1111/J.1445-5994.1997.TB00950.X.
36. Alkhouri N, Alamiry MR, Hupertz V, et al. Spur cell anemia as a cause of unconjugated hyperbilirubinemia after liver transplantation and its resolution after retransplantation. *Liver Transplant*. 2011;17:349–350. https://doi.org/10.1002/LT.22242.
37. Gonzalez-Casas R, Jones EA, Moreno-Otero R. Spectrum of anemia associated with chronic liver disease. *World J Gastroenterol*. 2009;15:4653. https://doi.org/10.3748/WJG.15.4653.
38. Acharya GK, Liao HI, Frunza-Stefan S, Patel R, Khaing M. Autoimmune hepatitis: diagnostic dilemma when it is disguised as iron overload syndrome. *J Clin Exp Hepatol*. 2017;7:269–273. https://doi.org/10.1016/J.JCEH.2017.03.006.
39. Premkumar M, Aggarwal A, Mehtani R, et al. Role of hepcidin, altered iron metabolism and systemic inflammation in the pathogenesis of iron deficiency anemia, anemia of chronic disease, and iron refractory anemia in cirrhosis and ACLF. *J Clin Exp Hepatol*. 2022;12:S33. https://doi.org/10.1016/j.jceh.2022.07.093.
40. Gremida A, Paleti S, Perez ET, McCarthy D. Hemolysis in alcoholic liver disease: Zieve's syndrome. *Dig Dis Sci*. 2018;63:601–604. https://doi.org/10.1007/S10620-018-4938-2/FIGURES/2.
41. Cruz C, Bassett J, Torres D. Zieve's syndrome: autoimmune hemolytic anemia associated with alcoholic liver disease and hyperlipidemia: 643. *Off J Am Coll Gastroenterol | ACG*. 2014 Oct 1;109:S186. https://journals.lww.com/ajg/fulltext/2013/10001/zieve_s_syndrome__autoimmune_hemolytic_anemia.545.aspx.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2022.10.005.

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