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4 ***VIBRIO FLUVIALIS* – UNUSUAL CASE**
5 **OF CELLULITIS LEADING TO SEPSIS**
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8 **ABSTRACT**

9 *Vibrio fluvialis*, an enteric, gram negative bacterium which can be isolated from dirty sewage/ sea
10 water contaminated with human and animal's faeces. Infections with this unusual organism can
11 cause cholera like bloody diarrhea and also wound infection. Here is a case report of skin and soft
12 tissue infection due to *Vibrio fluvialis* in patient having severe pedal oedema due to nephrotic
13 syndrome and right lower limb deep vein thrombosis .

14 Case report:A young male, farmer, presented with ascites, pedal oedema, puffy face due to
15 nephrotic syndrome.He developed skin and soft tissue infection resulted from skin atrophy and ulcer
16 due to pedal odema and right limb deep vein thrombosis .He had high grade fever, leucocytosis,
17 anaemia, hypoproteinemia, right leg cellulites and features of sepsis requiring wound debridement .
18 He was not on steroids and was not immuno-deficient. He was diagnosed to have Nephrotic
19 syndrome due to minimal change disease.

20 **Conclusion:** *Vibrio fluvialis* infection can occur due to wound contaminated with sewage water
21 resulting into life threatening skin and soft tissue infection and sepsis.

22 **Key words:** *Vibrio fluvialis* infection, skin and soft tissue infection, sepsis,Nephrotic syndrome
23

24 INTRODUCTION

25 *Vibrio fluvialis* is an emerging infectious diseasecausing pathogen.^[1]
26 It is one of the pathogen posing potentially a serious threat to public
27 health, due to multi-drug resistance and clinically challenging
28 infections.^[2]

29 The emerging pathogenic species of many bacteria have been posing
30 serious threat to public health. There is complex interaction between
31 environmental factors and industrialized world. In developing nations
32 like India,waterbodies are contaminated with sewage water, cattle
33 manure, household and industrial waste effluents. These waterbodies
34 serve as raw water sources to municipal water treatment
35 systems.^[3]Water contaminated with animal, human faeces and sewage
36 have been identified as potential sources of pathogenic bacteria.^[4]

37 *Vibrio Fluvialis* is an emerging pathogen of marine milleu, which
38 flourishes when temperature (warm) and salinity favours its
39 proliferation.^[5] It has become medically important pathogen as it has
40 been found to cause illnesses like cholera and rarely skin infections,
41 which are very challenging for clinicians to treat.^[2] It has not just
42 been found as a free living bacteria but also attached to various biotic
43 and abiotic structures.^[6] This complex property of forming biofilm
44 contributes to its survival against environmental stressors.^[6,7] As such
45 vibrio species can survive for a long time and adapt well to common
46 stressors encountered in natural ecosystem like lack of nutrients, by
47 changing their cell physiology and morphology.^[7,8] There is a state
48 called viable but non culturable (VBNC) where some bacterial species
49 adapt strategies under stressful conditions from which these can
50 recover themselves when optimal conditions are restored.^[8,9] Such
51 state has been observed in many vibrio species including historically
52 important human disease causing pathogens like *V.Cholerae*,
53 *V.parahemolyticus* and *V.vulnificus*.^[9] Similar mechanism has been
54 observed in this unusual and less studied pathogen, *V.fluvialis*, which
55 can maintain its virulence under hostile conditions and still be
56 pathogenic to humans.^[10]*V.fluvialis* related illnesses includes

Comment [jiv1]: Mostly, *V. cholera* shows more symptoms of dormancy, however *V. fluvialis* as marine pathogen should be growth in media with 2% NaCl

Comment [jiv2]: italics

57 gastroenteritis, cellulitis and primary septicaemia.^[11] There have been
58 identifiable host factors that can predispose to development of serious
59 infection with this bacterium, which includes alcoholic liver disease,
60 immunocompromised states like HIV/AIDS, diabetes, iron overload
61 and primary immunodeficiencies.^[11]

62 We are reporting an unusual case of young male having nephrotic
63 syndrome, deep vein thrombosis of leg and skin and soft tissue
64 infection caused by *vibrio fluvialis* leading to sepsis.

65 **CASE REPORT**

66 A 21 year- old male, farmer by occupation with no
67 comorbidities presented with complaints of generalized abdominal
68 pain with distension associated with facial puffiness and bilateral
69 pedal edema since the past 2 months and recent onset of right lower
70 limb pain with bullae initially and later becoming necrotic and
71 associated with high grade fever. Patient was admitted with clinical
72 diagnosis of nephrotic syndrome with cellulitis. He denied any history
73 of addictions, prior hospitalizations and relevant past medical history.

74 The patient appeared sick on examination, was febrile had
75 tachycardia, hypotension and tachypnea. He was cooperative,
76 conscious and oriented to time, place and person. Pallor was
77 observed, so was grade 3 pitting pedal oedema. There was moderate
78 ascites with grade II splenomegaly and pleural effusion. His right
79 lower limb was painful, discoloured and tense without regional
80 lymphadenopathy. The cellulitis was rapidly progressive from mere
81 swelling to formation of bullae and tissue necrosis within 24-36 hours
82 (Figure 1 and 2).

83 On laboratory investigation, following were yielded - haemoglobin
84 11.4 g/dl, total count – 18000/cu.mm (93% neutrophils), Erythrocyte
85 sedimentation rate – 90 mm/hr, C- reactive protein – 108 mg/dl, serum
86 albumin 2.0 mg/dl. Urinalysis revealed foamy urine with specific
87 gravity of 1.016, albumin 4+, and few fatty casts were seen on urine
88 sediment. 24 hour urinary proteins was 4.7 grams.

89 His lipid profile was deranged with hypercholesterolemia and
90 hypertriglyceridemia. Rest of the routine blood investigations
91 including renal function tests were within normal. He was tested
92 negative for HIV, hepatitis B, C and Syphilis. RT-PCR for COVID 19
93 was done and found negative. Haemoglobin electrophoresis was done
94 and didn't reveal any hemoglobinopathy. Abdominal ultrasonography
95 revealed mild splenomegaly and moderate ascites. Bilateral moderate
96 pleural effusion was seen on chest x-ray and chest sonography. The
97 right lower limb arterial and venous doppler was done which was
98 suggestive of subcutaneous oedema with partial thrombosis of
99 saphenous vein. ECG and 2-D Echocardiography was
100 normal. Antinuclear antibody (ANA) test and ANA profile was
101 unremarkable.

102 The total leukocyte counts raised to 30,000 /cu mm on day 3 of
103 admission and patient had continuous high grade fever with
104 hypotension. He had septic shock with metabolic acidosis. Empiric
105 para-renal antibiotic was started on admission which included
106 linezolid and meropenem. Blood cultures were sent. Surgical
107 debridement of the foot was done and tissue specimen was sent for
108 culture. Blood cultures showed no growth until day 7 and was
109 considered negative. Tissue culture showed gram negative rods
110 identified as *Vibrio fluvialis* sensitive to gentamicin and doxycycline.
111 The antibiotics were switched as per antibiogram report. Patient was
112 also given injectable human albumin 20% as infusion. He kept
113 deteriorating with until day 10 (Figure 3-5). Dressing was done daily
114 and the wound healing was observed closely. There was significant
115 reduction in the edema and development of granulation tissue at the
116 wound site by day 15. He recovered from septic shock and total
117 leukocytes counts started falling (10,000 by day 17). He was
118 discharged by day 25 after recovering from sepsis with healing
119 wound.

Comment [jiv3]: spaces

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122 Figure 1&2 : day 1-3 : Rapid necrosis of tissue.

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Figure 3- day 4- progression of infection



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128 Figure 4 : Day 7 – Granulation tissue

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133 Figure 5:Day 10 - Post debridement

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135 DISCUSSION

136 The skin and soft tissue infections are more commonly caused by
137 gram positive organisms like staphylococci and streptococci which are
138 part of skin and mucous membrane flora.^[12] Most of these infections
139 are minor in nature but may progress to complicated infection leading
140 to tissue necrosis and sepsis when other underlying risk factors are
141 present such as diabetes mellitus and immunodeficient states.^[12,13] It
142 becomes highly challenging to differentiate which of these patients
143 require immediate and surgical management. The affected area
144 becomes dysfunctional and depending on comorbidities the infection
145 can progress rapidly, may develop sepsis which can lead to death
146 also.^[13,14]

Comment [jiv4]: Gram-negative staining picture should be provided

147 Incase presented above, the patient was non- diabetic, non- alcoholic
148 individual with nephrotic syndrome and peripheral venous thrombosis
149 in right lower limb with secondary cellulitis by a rare unusual
150 pathogen. *Vibrio* species are a rare cause of necrotizing soft-tissue
151 infections and primary sepsis, which are likely to occur in patients
152 with hepatic disease, diabetes, adrenal insufficiency, and
153 immunocompromised conditions.^[2] Among them, most important
154 *vibrio spp* which causes skin and soft tissue infection which often
155 require debridement and amputation are *Vibrio fluvialis* and *Vibrio*
156 *vulnificus*. *V. fluvialis* is associated with gastroenteritis and cholera like
157 illness and among extra-intestinal infections, it has been found to
158 cause haemorrhagic cellulitis, cerebritis, peritonitis and primary
159 septicaemia.^[15] Acute gastroenteritis which rapidly progresses to
160 shock in 4 to 24hours, whereas cellulitis which rapidly causes local
161 tissue necrosis associated with haemorrhagic bullae, further causing
162 obliterating vasculitis and vascular necrosis requiring tissue
163 debridement.^[15] *V. fluvialis* associated cellulitis can occur when an
164 abraded area of skin is inoculated by bathing in marine waters where
165 this bacteria thrives.^[16] As it has been documented that the prevalence
166 of this bacteria is high in aquatic realm, the exposure to its infection
167 in our patient could have been during farming practices where dipping
168 feet in water is required.

169 Very few cases have been reported around the world, most have been
170 from Asian and developing countries and having the history of
171 exposure to marine environment and having chronic illness or in an
172 immunocompromised state. Majority of the cases required tissue
173 debridement/amputation and inotropic support. As in our case
174 described above, patient had immunodeficient state with
175 hypercoagulability due to loss of proteins in urine secondary to
176 nephrotic syndrome. HuangKuo-Chin and Wen-Wei HsuR, reported
177 a case of *vibrio fluvialis* in a 45-year-old male following exposure to
178 brackish water causing haemorrhagic cellulitis and cerebritis which
179 required amputation and causing death even after aggressive
180 management.^[15] Another case of 47 years old Asian fisherman

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Comment [jiv9]: A TCBS media and O-129 should be provide to discriminated *V. cholera* from the species determination or provide an additional material to confirm *V. fluvialis* species.

181 reported by Tsai Yao-Hung et al in known case of Hepatitis B
182 infection with exposure to sea water on an open wound who presented
183 with swelling and bullae of lower limb, which progressed to tissue
184 necrosis and an above knee amputation was performed to save the
185 patient.^[16] Our patient had non haemorrhagic bullae on admission
186 and which rapidly progressed to tissue necrosis and required
187 debridement. We managed the sepsis in our patient aggressively with
188 multiple tissue debridements, and timely initiation of tissue culture
189 sensitive antibiotics, which perhaps helped in containment of the
190 infection and controlling sepsis.

191 A retrospective study of 13 patients done by Tsai Y. *et al* on systemic
192 vibrio infection presenting as necrotising fasciitis and Sepsis revealed
193 that all of these patients had history of contact with sea water or raw
194 sea food and all of them had one or other comorbid conditions like
195 cirrhosis, Diabetes mellitus and chronic kidney disease. 12 patients
196 required tissue debridement or limb amputation with death in 5
197 patients. The risk factors identified for high mortality included low
198 systolic blood pressure and leucopenia on admission.^[17] In our case
199 our patient denied exposure to sea water and marine life and he was
200 vegetarian by diet, and most possible exposure is from the water used
201 for agricultural purposes contaminated with vibrio.

202 These bacteria are thermostable and have hemolysin as virulent
203 factor. It was found by Han et al that hemolysin from *V. fluvialis*
204 forms pores in membranes of erythrocytes inducing osmotic lysis.^[18]
205 Their strategies against starvation helps them survive for long term in
206 sea water indicating that these species are endemic in marine
207 environment and can infect marine hosts when conditions are
208 favourable to them.^[19]

209 Antimicrobial resistance is commonly reported in vibrio species.
210 Culture report of this cited case had *V. fluvialis* resistant to meropenem,
211 cephalosporins and other beta-lactams. The *V. fluvialis* species isolated
212 from diarrheal patients in Kolkata were resistant to fluoroquinolones
213 and beta-lactams. It was due to mutations of quinolone resistance-
214 determining region (QRDR) of *gyrA*.^[20]

Comment [jiv10]: Check italics and spaces

215 We treated our patient with doxycycline and gentamicin. The
216 empirical antibiotic of choice can be debated as this pathogen has
217 multiple resistance patterns. Injectable doxycycline 100 mg 12 hours
218 apart has been recommended by Haq and Dayal in cases with high
219 index of suspicion, though it is never a choice for empirical therapy
220 for sepsis treatment guidelines.^[21]

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222 This concise case report aims at providing knowledge regarding such
223 emerging pathogens and diseases caused by them, as there is paucity
224 of literature and reported cases about these pathogens. Also it
225 highlights the importance of early debridement, early cultures and
226 early introduction of appropriate antibiotics as per the sensitivity and
227 supportive care will significantly reduce the mortality of patients.

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230 **CONCLUSION**

231 *Vibrio Fluvialis* causing skin infection and sepsis is uncommon with
232 very few cases reported worldwide. In cases of rapid progression of
233 the symptoms leading to tissue necrosis and haemodynamic instability
234 in comorbid patients, must consider and evaluate for Gram negative
235 sepsis due to such vibrio species.

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UNDER PEER REVIEW