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Concomitant ulcerative colitis and Usher syndrome in a Pakistani patient: A novel case report

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Abstract

Ulcerative colitis (UC) and Usher syndrome (USH) are debilitating diseases, compromising quality of life. Globally, half a million cases of UC have been reported, whereas USH is the leading cause of genetic deaf-blindness worldwide. The combined occurrence of both these diseases together is extremely rare. In this one-of-a-kind case report, we discuss the implication of a limited resource-setting on the diagnosis of those diseases. A 33-year-old Southeast Asian male, a known case of hepatitis C presented with a chronic reduction of vision and hearing loss and an acute presentation of loose stools, abdominal pain, and weight loss for 4–7 months. Raised inflammatory markers were reported with a C-Reactive Protein (CRP) level of 64.8 mg/dL. Ultrasound of the abdomen revealed mild abdominopelvic ascites. Colonoscopy showed multiple polyps and was biopsied to have fragments of colonic mucosa with moderate active colitis along with ulcer slough. A Computed Tomography (CT) scan with contrast of the abdomen and pelvis suggested thickened bowel, findings all suggestive of UC. For hearing and sight loss, fundoscopy showed retinitis pigmentosa (RP), and pure tone audiometry suggested bilateral sensorineural hearing loss. A probable diagnosis of mild UC and type II USH was made on clinical examination, radiological imaging, and histopathological sampling. UC and USH have genetic mutations that contribute to the disease manifestations; however, none occur mutually. UC has ophthalmic extraintestinal manifestations, but RP, which is the main reported manifestation in USH, is rarely reported in UC. Maximum efforts were exercised in diagnosing and managing the patient effectively despite the limited resources available. The coexisting USH and UC diagnosis in this patient presents as a rare case. More research is needed to further determine a shared immunological basis of the two disease etiologies and therapeutic advancement.

Keywords

Ulcerative colitis, Usher syndrome, case report

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease, with an estimated 5 million cases present worldwide, with a progressively increasing incidence, presenting with bloody diarrhea, abdominal pain, fecal incontinence, and fatigue as intestinal signs and symptoms with erythema nodosum and pyoderma gangrenosum as cutaneous, anterior uveitis or episcleritis as ocular, peripheral arthropathy, and anemia as the main extraintestinal manifestations (EIMs). Diagnosis is based on clinical findings, lab parameters, endoscopic findings, and histopathology. Treatment for remission includes corticosteroids and 5-aminosalicylic acids (5-ASA), whereas maintenance treatment is done with 5-ASA drugs, biologics, thiopurines, and small molecules like Janus kinase inhibitors. Definitive treatment can be achieved with a proctocolectomy for patients not responding to medical management.[1,2]

Usher syndrome (USH), inherited in an autosomal recessive pattern, is the leading cause of genetic deaf-blindness, affecting around 3–6.2 people per 100,000.[3] It is a syndromic ciliopathy and is characterized by retinitis pigmentosa (RP) and sensorineural hearing loss (SNHL) with three different

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Table 1. Types of Usher syndromes.

Type of USH	Genetic mutation	Loss of sensorineural hearing	Impairment of balance	Loss of vision	Treatment
USH Type 1	MAYO7A, USH1C, USH1G	Severe, congenital	Absent vestibular response	Average diagnostic age: second decade	• Cochlear implants or hearing aids • Vision aids
USH Type 2	USH2A, WHRN	Moderate to severe, congenital	Normal vestibular response	Average diagnostic age: third decade	
USH Type 3	CLRN1	Variable, progressive	Normal or delayed vestibular response	Average diagnostic age: variable	

Source: Data included from studies.[3,4,8]
USH: Usher syndrome.

clinical subtypes depending on the age of onset, the severity of symptoms, and the presence or absence of vestibular dysfunction. USH Type 1 is the most severe subtype, characterized by symptoms starting early with prelingual SNHL, early onset of RP, and the presence of vestibular dysfunction. USH Type 2 is the most reported type and has moderate-severe SNHL with RP occurring after ten years of age and no vestibular symptoms. USH Type 3 is the rarest, with SNHL arising postlingually, variable onset of RP, and may or may not have vestibular dysfunction patients that do not fit into these categories are classified as atypical USH (Table 1).[4]

Our case report is based on a young patient with chronic diarrhea who was diagnosed with UC and USH on workup, coexistence of which is rare. This case report conforms to the CARE guidelines.[5]

Case presentation

A 33-year-old male with a known case of hepatitis C presented with the following:

(1) Chronically gradual, progressive hearing loss and bilaterally decreased visual acuity since childhood.
(2) Loose stools with 5–6 diarrheal bouts daily for 7 months.
(3) Generalized crampy abdominal pain for the last 4 months.
(4) Unintentional weight loss for 4 months.

Initial laboratory workup revealed an elevated CRP of 64.8 mg/dL, decreased total protein levels of 5.1 g/dL, and serum albumin of 1.7 g/dL. Stool culture remained unremarkable.

A relevant abdominal examination revealed no significant findings.

Radiological imaging included:

(i) Abdominal ultrasound, which showed mild abdominopelvic ascites.
(ii) Oesophagoduodenoscopy, which remained unremarkable.
(iii) Colonoscopy, which showed multiple polyps suggestive of inflammatory polyps, which led to the recommendation of contrast-enhanced CT abdomen and pelvis and biopsy sampling of the colonic polyps (Figure 1).
(iv) Contrast-enhanced CT of the abdomen and pelvis showed multifocal circumferential edematous mural thickening of the large bowel, starting from the anal canal up to the descending colon. The transverse and descending colon appeared ahaustral. Multifocal polypoid growths were seen arising from the large bowel, starting from the rectum up to the transverse colon. One of them measured 1.4 cm at the distal transverse colon. The rest of the scan appeared normal (Figure 2(a), (b), and (c)).

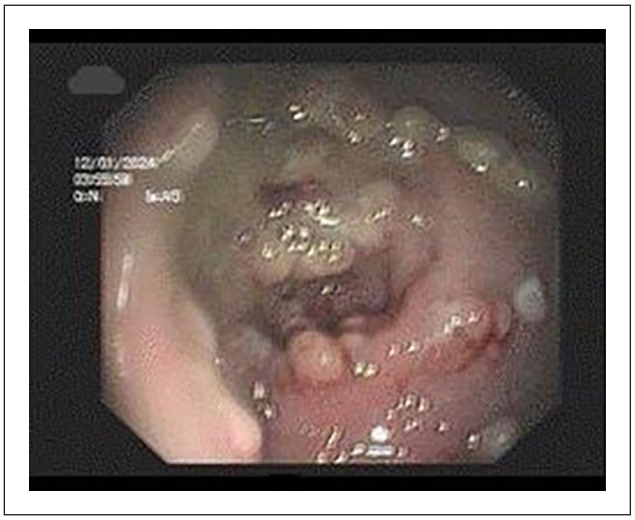

Figure 1. Multiple polyps seen throughout the colon.

Histopathology of the biopsy samples taken from the colonic polyps on colonoscopy showed fragments of colonic mucosa with moderate active colitis along with ulcer slough.

Based on the results revealed via diagnostic modalities available to us in a resource-limited setting, a probable diagnosis of mild UC was made, and the patient was managed accordingly.

To determine the cause of gradual hearing and vision loss, it was noted that he had bilaterally decreased visual acuity.

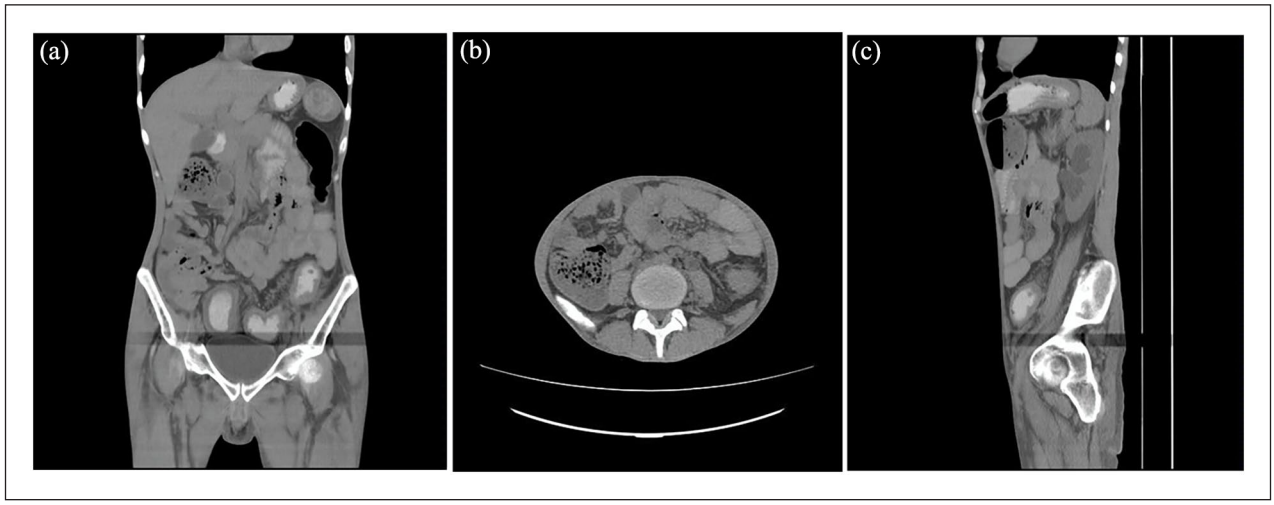

Figure 2. CT abdomen and pelvis with contrast showing circumferential intestinal wall thickening, mural stratification, extramural deposition of fat, and stricture though not widely appreciated. (a) Coronal plane. (b) Axial plane. (c) Sagittal plane.

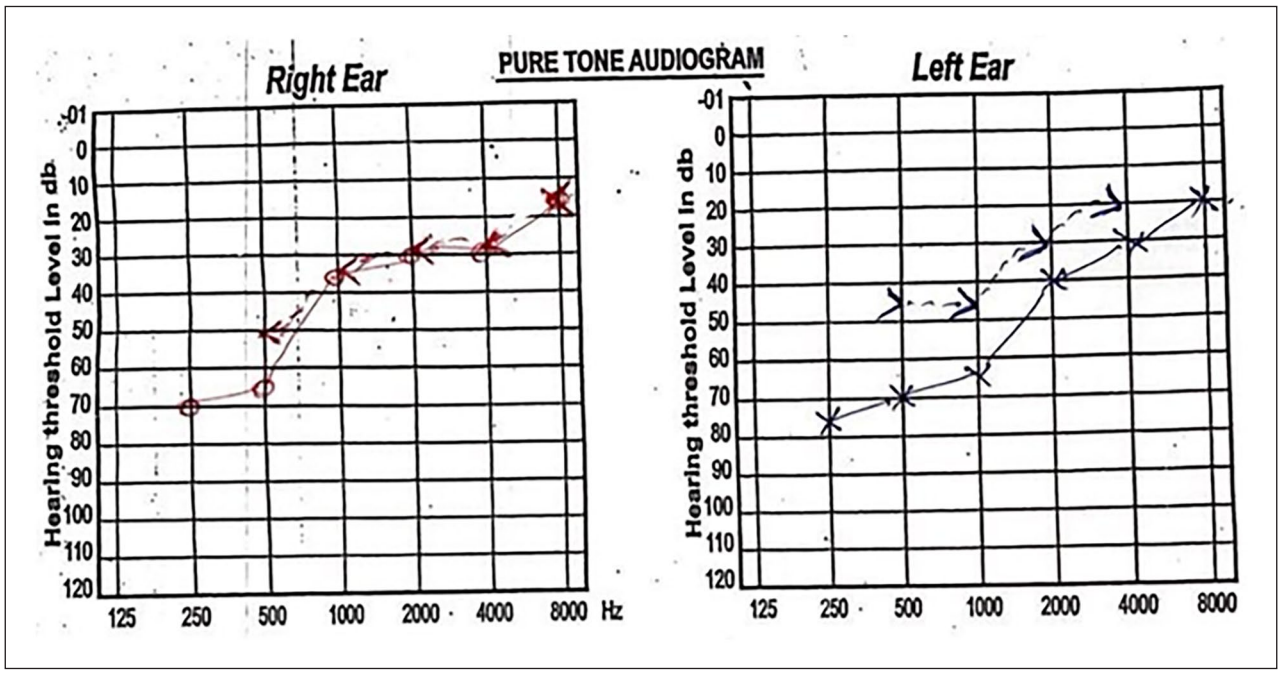

Figure 3. Pure tone audiogram showing sensorineural hearing loss on low frequency.

Ophthalmology was consulted for his vision loss, and fundoscopy showed RP. Similarly, otorhinolaryngology was consulted for his hearing loss. Pure tone audiometry was done, and bilateral SNHL was observed (Figure 3).

It is to be noted that his past medical history was significant for gradual, progressive hearing loss and bilateral vision loss, both of which started during childhood. His family history remained positive for similar symptoms as his older set of twin brothers also reported gradually decreasing hearing and vision. The patient was labeled to have type II USH.

A differential diagnosis of USH was made based on his clinical findings. Genetic analysis for a confirmatory diagnosis of USH could not be done due to the financial constraints present in our resource-limited setting.

Discussion

Our patient presented with a rare occurrence of two combined disease etiologies, that is, UC and USH. The coexisting manifestation of the two disease spectrums leads to questions regarding their genetic linkage.

According to Sarlos et al., not only is UC associated with Th17 (IL-17) and a modified Th2 response (IL-13, IL-5, and IL-9), but recently genome-wide association studies have identified many novel single nucleotide polymorphisms for UC.[6] In a resource-limited region like Pakistan with an approximate Gross Domestic Product (GDP) per capita of USD 1600, many cases of UC remain undiagnosed due to a lack of necessary diagnostic facilities; however, the extent of its prevalence can be reflected in a retrospective cohort in the years 2013–2020, when 11.55% (165 out of 1428) of the patients who underwent sigmoidoscopy had UC.[7] As for USH, nine causal genes encoding various proteins expressed in the inner ear and retina, including MYO7A, USH1C, PCDH15, CDH23, and USH1G for USH1, USH2A, ADGRV1, and WHRN for USH2, and CLRN1 for USH3 are reported, however the mutations could not be deciphered for the said patient due to lack of necessary resources.[8]

Although identified, the genetic mutations existing for each disease remain unrelated to date; however, recent advances and further research may change the dynamics and decipher a shared genetic mutation for the two disease etiologies. The concurrence of UC and USH in Pakistan may point toward a greater pool of genetic mutations in the geographical region of Pakistan. According to a survey, 29.2 million people in Pakistan have phenotypically evident genetic mutations, owing to the intra-family unions in the form of consanguineous marriages. Pakistan genetic mutation database also highlights 1000 mutations reported in 130 genetic diseases, thus also allowing the possibility of a shared genetic mutation for the concurrence of USH and UC.[9]

IBD also leads to EIMs as immune complex depositions may also manifest as leukocytoclastic vasculitis (LV) as an EIM.[10] EIM in the form of ophthalmic signs and symptoms is observed in 0.3%–13.0% of cases, of which 1.6%–5.4% occur in UC.[11] These may vary between episcleritis (2%–5%) and uveitis (0.5%–3.5%), affecting vision; however, RP is rarely reported, which is the core reason for vision loss in USH, hence again negating a link between the two disease etiologies.[12,13] However, UC patients may exhibit signs and symptoms of SNHL attributed mainly to autoimmune inner ear disease, like the bilateral SNHL seen in USH.[14] A recent study has identified the possible role of inflammation in RP like UC and discusses the possible role of immune modulating therapies targeting TNFα signaling, TLR signaling, chemokine signaling, and JAK/STAT signaling, thus pointing toward a possible genetic linkage between the two diseases.[15]

Since the patient presented with loose, watery stools with concurrent abdominal pain, various differentials were considered, including microscopic colitis, further divided into histological subtypes (1) collagenous colitis and (2) lymphocytic colitis; inflammatory bowel syndrome; infectious etiologies; drug therapies; and celiac disease to name a few. Familial adenomatous polyposis (FAP) was also considered as a differential based on the presence of polyps on colonoscopy; however, the mere presence of polyps, not quantified enough, did not qualify as a diagnostic marker necessary for FAP. Hence, polyps were suggested to be more of an inflammatory histology.[16] Histopathological reports reported basal plasmacytosis and villous surface irregularity, in conformity with UC, more than any other suggested differential.

The hierarchy of diagnostic criteria present in our setting with limited resources, only blood tests, stool cultures, endoscopy, colonoscopy, histopathology, and radiological imaging, including abdominal X-rays and CT abdomen with contrast, could be offered to the patient. The severity of UC is clinically determined based on the Mayo criteria.[2] Since our patient had loose, watery, and not bloody stools, combined with other factors, he was considered to have a mild form of UC.

While treatment remains conventional for patients, surgery remains available as the definitive treatment in the form of subtotal colectomy, permanent ileostomy, ileoanal pouch, and ileorectal anastomosis in severe cases.

Adverse events associated with medical therapy include reduction in bone mineral density with Budesonide, myelotoxicity, pancreatitis, non-melanoma skin cancers and lymphomas with thiopurines, VTE risk associated with Tofacitinib, increased susceptibility to infections associated with anti-TNF medications and with surgical options, may include anastomotic leakage, disturbed bowels, inflammatory rectal stump, and associated mental distress after the procedure.[17] The currently trialed therapies, including JAK2 inhibitors and fecal microbiota transplantation, may change the dynamics of managing UC.[2]

Our patient also presented with Type 2 USH. Globally, it is the most reported type. According to Bonnet et al., patients typically have a downward-sloping audiogram, mild congenital SNHL for low frequencies, and severe SNHL for higher frequencies.[18] Hearing aids or cochlear implants can somehow alleviate auditory sensory deprivation; however, in our resource-limited setting, none of these could be offered to the patient.[19] Since in our setting, advanced therapeutic regimens including gene therapies cannot be offered due to financial constraints, thus the patient is clinically assessed on follow-ups.

Limitations

Our case reports present with the following limitations:

1) Stool calprotectin could not be obtained as the clinicians, in a resource-limited setting, tried to proceed with the more diagnostically significant radiological imaging as stool calprotectin, though sensitive, remains nonspecific for IBD.[20]
2) Histopathological pictures of colonic biopsies could not be retrieved.
3) Clinical follow-up data could not be retrieved.

Conclusion

The coexisting USH and UC diagnosis in this patient is present as a rare case. Maximum efforts were exercised in diagnosing

and managing the patient effectively despite the limited resources. However, further research is also necessary to decipher a shared immunological basis for the two disease entities and determine the most effective therapeutic modalities, which may limit the disease if not therapeutically viable enough to cure the patient.

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Author contributions

FS wrote the introduction and case presentation, and reviewed and edited the manuscript; AA wrote the abstract and discussion; SA reviewed and edited the manuscript.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declaration of conflicting interests

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Ethics approval and consent to participate

The ethics committee of Dow University of Health Sciences has waived off the prerequisite of approval due to the observational nature of this case report. Informed consent was taken from the patient.

Ethics approval

Ethical approval to report this case was obtained from the ethics committee of Dow University of Health Sciences.

Consent for publication

Written informed consent was taken from the patient for the publication of this case report and accompanying images.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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