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Can Autoimmune Encephalitis Occur with Negative Markers? A Rare Case Report

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Abstract

In our case, we present a case of a 27-year-old male who presented with progressively worsening altered mental status and seizures. Over the course of his admission to the hospital and intensive care unit, laboratory testing failed to find an offending agent to his presentation. Testing did result in the diagnosis of encephalitis, but an underlying cause was not found. After careful exclusion of bacterial, viral, and other types of encephalopathy, autoimmune encephalopathy was diagnosed despite the absence of commonly used markers of autoimmune encephalopathy. The presentation and symptoms of our patient led to a wide range of differentials, and a high index of suspicion was needed throughout his admission in order to obtain the appropriate tests. Although appropriate testing might be ordered, due to the sensitivities and specificities of all laboratory tests, these objective tests do produce false negative results at times. It is in these times that one must weigh the physical exam, clinical judgment, and the process of elimination to diagnose an underlying pathology. Autoimmune Encephalitis diagnosis can be broken down into possible, probable, and definitive diagnoses based on antibody testing results. In this case, we present a patient with probable autoimmune encephalitis that failed to yield positive autoimmune markers after extensive testing of other possible causes of encephalitis.

Keywords

Autoimmune Encephalitis, Seizures, Paraneoplastic Syndrome, Encephalitis, Autoimmune

1. Introduction

Autoimmune encephalitis (AIE) is an inflammatory disease of the brain, characterized by a broad clinical spectrum making it difficult to recognize at times. Clinically, this disease can initially present with psychosis, seizures, cognitive

deficits, changes in behavior, dysautonomia, and altered mental status but can also lead to life-threatening presentations as severe as a comatose state, encephalopathy, and status epilepticus. AIE is associated with autoantibodies that target both extracellular and intracellular neuronal components. Antibodies against extracellular neuronal components, such as cell surface antigens, can alter synaptic transmission and neuronal excitability. Antibodies on the intracellular antigens are T-cell mediated and lead to detrimental progression of the disease [1]. AIE could be a paraneoplastic syndrome and can often be diagnosed prior to the underlying malignancy. More specifically, malignancy tends to lead to AIE caused by the Intracellular antibodies and the T-cell mediated damage; nevertheless, any patient with AIE should be screened for underlying malignancy. The diagnosis of AIE is most commonly confirmed with autoantibody testing. These autoantibodies can attack cell surface antigens, synaptic transmission, and intracellular components of the neurons. Like all tests, though, no confirmatory test is accurate and precise all the time, and for that reason, false negatives are possible. In this case, a 27-year-old male presented to the emergency department with altered mental status and was later diagnosed with AIE through a protracted clinical course with the reasonable exclusion of alternative causes.

2. Case Presentation

A 27-year-old male with no known previous medical history presented to the emergency department for altered mental status. The patient's family described a grand-mal seizure activity, including shaking of all extremities, foaming at the mouth, and eye-rolling. Upon further history taking, it was noted that he had been seen five days prior at an urgent clinic for a fever and was diagnosed with an unknown viral infection and given azithromycin. The patient had a second attack of seizure in the emergency department and was given Keppra and antibiotics for possible meningitis or encephalitis. The patient had continuous rigors throughout his admission. His mental status continued to wax and wane throughout his hospital course, regardless of intervention. He later developed status epilepticus that warranted immediate airway protection and intubation. He was arousable after intubation but would develop rigors throughout his whole body when aroused.

Over the course of his admission, the patient had a lumbar puncture, electroencephalogram (EEG), magnetic resonance imaging (MRI), and other special tests that included testing for Lyme disease, mycobacterial infections, toxoplasma, and sarcoid. Lumbar puncture revealed a white blood cell count of 11 cells, protein of 26 mg/dL, and glucose of 75 mg/dL. The EEG showed non-specific encephalopathy with no evidence of seizures or epileptogenic potentials. A follow-up video EEG had comparable results. MRI of the brain revealed interval development of restricted diffusion with hyperintensity in the left hippocampus, highly suggestive of possible encephalitis (**Figure 1**). All other special tests yielded negative results. The autoimmune panel resulted in positive glutamic

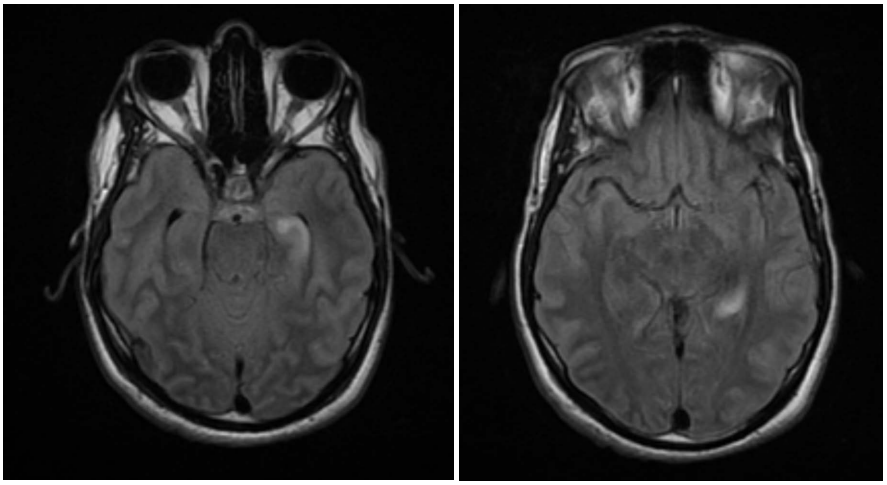

Figure 1. MRI of the brain revealing hyper-intensity in the left hippocampus, highly suggestive of possible encephalitis.

acid decarboxylase, which has low specificity to autoimmune encephalitis but was negative for N-methyl-D-aspartate (NMDA) receptor antibodies. Other autoantibodies in CSF such as AGNA-1, ANNA 1-3, CRMP-5-IgG and PCA-Tr were also all found to be negative. The patient continued to be monitored in the medical intensive care unit. When consulting with the neurologist, the patient was given dantrolene to cover the possibility of a neuroleptic malignant syndrome. The patient was also covered with wide-spectrum vancomycin, ceftriaxone, Bactrim and acyclovir, and steroids for infective causes of encephalitis. Due to a lack of clinical improvement, non-convulsive status epilepticus was highly suspected. Without an apparent cause of encephalitis, the patient was diagnosed with autoimmune encephalitis and received a five-day course of 25 g intravenous immunoglobulin (IVIG) daily and a six-day course of 1 g of methylprednisolone daily, to which he responded well. From the literature, establishing the diagnosis of AIE on antibodies results is not reliable, as first, it might take weeks for the results to come back, and secondly, negative results do not exclude AIE.

3. Discussion

Encephalitis, a state of inflammatory disorder in the brain, encompasses a wide variety of differential diagnoses. Encephalitis has been attributed mainly to infectious causes; however, over the past decade, AIE has been increasing in incidence, which is about five per hundred thousand. Research in AIE has been evolving in recent years in regard to diagnosis and treatment. The International Encephalitis Consortium 2013 diagnostic criteria for encephalitis of possible infection vs. autoimmune necessitates the presence of altered mentation lasting at least twenty-four hours with no other identifiable cause. Confirmation would occur if the patient meets at least 3 minor criteria: 1) fever in the last 3 days, 2) new onset of focal neurological deficit, 3) CSF leukocytosis, 4) acute new abnormality is seen on neuroimaging characteristic of encephalitis, or 5) EEG ab-

normalities consistent with encephalitis [2]. Those five criteria can help differentiate autoimmune causes from infectious causes in both adults and children. Certain antibodies in the circulation and the response to immunotherapy are manifested in AIE. Graus et Titulaer [3] concluded that it is not realistic to have antibody testing as a part of early diagnostic criteria for the evaluation of AIE due to many reasons. First, antibody testing can take many weeks to come back, depending on the hospital's capabilities. Second, negative antibodies result does not negate or exclude the diagnosis of AIE. Third, a positive result does not confirm the diagnosis. They also concluded that the response to immunotherapy is not practical for different reasons, for example, the lag in time between the treatment and the effect and the different responses for AIE patients to the same treatment. Graus et Titulaer developed new diagnostic criteria for AIE by identifying possible autoimmune encephalitis, which is not dependent on neuronal auto-antibody status, which resulted in the establishment of three levels of clinical evidence for AIE: possible and probable (for which auto-antibody test is not needed in most cases) and definite (for which auto-antibody test is needed).

AIE can mimic infectious encephalitis in neurological and psychiatric symptoms; however, fever and CSF changes may be absent. Severe brain injury in AIE is usually acute (less than six weeks) and results from the uncontrolled production of anti-neuronal antibodies against cell surface (CSAab), synaptic (SyAab), or intraneuronal (INAab) antigens [1]. The CSAab (anti-N-methyl-D-aspartate receptors) disrupts neurotransmission and may result in cell death [4]. Like many autoimmune diseases, the progression of the disease can vary from one patient to another, but early detection and treatment can lead to a greater prognosis. Clinical presentations include seizures, motor weakness, behavioral changes, and abnormal movements [5]. AIE can present with variable symptoms and signs and does not always include all available presentations. However, seizures are the most common symptom [5] [6]. For instance, refractory status epilepticus is more strongly associated with Anti-NMDA (ovarian and testis teratoma), Anti-AMPA (thymoma, lung, and breast cancer in 65%), and anti-GABA (in thymoma). Although associated with some cancers, AIE can also afflict patients without cancer predisposition [1]. Sleep disturbance is very common and can get severe. Even with appropriate treatment, it can persist later and leave a negative impact on the quality of life in AIE patients [7]. It is usually significant in patients with positive anti-IgLON5 and anti-NMDA receptor encephalitis. Where primary schizophreniform psychosis arises due to genetic interaction with the environment, secondary schizophreniform psychosis occurs due to organic insult, and it includes autoimmune psychosis, which presents with acute onset of polymorphic psychotic symptoms, including (hallucination, catatonic reactions, paranoid, personality disorders, etc) commonly associated with other neurological signs (fever, seizure, movement disorder, etc.); however, can be isolated in both acute or relapse stages of AIE. In children, it's more complicated to diagnose AIE because children present with different symptoms, especially

behavioral manifestations, which are very complex and evolving at this time, which reflects in late diagnosis with worse outcomes. Regardless, all patients with AIE should be screened for tumors while considering the clinical presentation [8].

AIE is commonly treated with immunosuppressive therapy, and the prognosis depends on the response to the therapy. Regardless, early immunotherapy treatment is recommended for a better prognosis [8]. In refractory conditions, where standard steroids fail, intravenous immunoglobulin, plasma exchange (PLEX), and immune-modulating (including Rituximab and cyclophosphamide [9] [10] [11] can help. MRI and imaging studies can help in treatment as well; for example, in paraneoplastic autoimmune limbic encephalitis, tumor resection can manage the encephalitis. Recovery in AIE usually takes prolonged time, and relapses are common to occur, despite the effectiveness of many immunosuppressive therapies. Therefore, specific immunotherapy coupled with supportive target-specific therapy can help control the symptoms and shorten the disease course. The approach can also maintain long-lasting disease stability and decrease the incidence of relapses. Targeted immuno-suppressive receptor blockers, which can cross the blood-brain barrier, have shown great results. For example, daratumumab has shown clinical significance in the depletion of autoreactive plasma cells (receptor targets) in AIE [12]. Treating neurological and psychiatric symptoms has been proven to decrease morbidity and mortality. Antipsychotics and electro-convulsive therapy have succeeded in treating different psychiatric presentations of AIE. Intensive care unit management may be existential in treating life-threatening conditions like status epilepticus.

4. Conclusion

Clinicians today rely heavily on their clinical knowledge, judgment, and intuition alongside tests to guide patient care. At times, this becomes difficult as no objective tests exist with sensitivities and specificities of 100%. When objective tests fail to aid in the diagnosis, a clinician can diagnose by ruling out other causes while waiting for other time-consuming special tests. In this patient's case, standard tests failed to confirm autoimmune encephalitis. Without a clear etiology of the encephalitis based on routine testing, one should rely on clinical and distinct MRI features to diagnose autoimmune encephalitis while waiting for special test results and confirmation. Prompt recognition of characteristic presentations of these autoimmune encephalitides can lead to earlier treatment and prevent further irreversible brain degeneration [13].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Atypical Hemolytic Uremic Syndrome in a Patient with Acute Promyelocytic Leukemia: A Case Report

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Abstract

Introduction: Acute Promyelocytic Leukemia (APL) is highly associated with hemostasis alterations. The atypical hemolytic uremic syndrome (aHUS) is a rare type of Thrombotic Microangiopathy (TMA) due to an overactivation of the alternative complement pathway. **Case Presentation:** A 48-years-old woman was diagnosed with APL and achieved molecular remission after induction therapy. During the second consolidation cycle she presented with TMA. She began treatment with plasma exchange plus corticotherapy but due to aggravation of symptoms Eculizumab was initiated. Thrombotic thrombocytopenic purpura, infections and drug toxicity causes were ruled out. There was no evidence of relapse of the APL. Genetic studies of the hereditary anomalies of the alternative complement pathway were negative and the decision of stopping Eculizumab was made. During maintenance therapy for the APL she presented a severe relapse of the aHUS, requiring dialysis. She re-started treatment with Eculizumab with a progressive hematologic recovery and improvement of renal function. She completed APL treatment without relapse of the leukemia for the moment and continues to be treated with Eculizumab. **Conclusion:** This is the first published case of coexisting aHUS and APL successfully treated with Eculizumab.

Keywords

Atypical Hemolytic Uremic Syndrome, Acute Promyelocytic Leukemia

1. Introduction

The acute promyelocytic leukemia (APL) represent the 10% - 15% of the newly

diagnosed acute myeloid leukemia cases and results from a balanced translocation, t(15;17) (q22;q12-21), which leads to the fusion of the promyelocytic leukemia (PML) gene with the retinoic acid receptor alpha (RARα) gene [1]. It is well known that this type of leukemia is highly associated with hemostasis alterations at the time of diagnosis, specially hyperfibrinolysis, disseminated intravascular coagulation, and thrombocytopenia [2] and hemorrhagic death remains the main cause of induction failure [3] [4]. However, with current treatments, the overall survival of this type of leukemia is high (>90% at 3 years) [5] [6] compared to other types of acute leukemias. The most important step in preventing bleeding complications is the prompt treatment with all-trans retinoic acid (ATRA), with or without arsenic trioxide (ATO) together with supportive transfusions and repletion of coagulation factors [3].

Atypical hemolytic uremic syndrome (aHUS) is a rare and severe type of thrombotic microangiopathy (TMA) with a reported annual incidence ranging from 0.23 to 1.9 per million population. In 40% - 60% of the cases there is a genetic component that results in the overactivation of the alternative complement pathway [7]. These mutations are in the genes that encode complement regulatory proteins, Factor H, Factor I, membrane cofactor protein, complement 3 (C3), Factor B or thrombomodulin. In other patients the physiopathology is characterized by the presence of anti-FH antibodies resulting in activation of the complement system.

Clinically, it is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment. Kidneys are the most vulnerable organs affected which is mainly due to a dysfunction of endothelial cell exacerbated by anaphylatoxins (C3a and C5a) produced during complement activation and the formation of microthrombi in the kidney vasculature [8]. The diagnostic is made by excluding other causes of TMA, demonstrating preserved ADAMTS13 function and searching germline variants in complement genes or autoantibodies against complement regulatory proteins, which are present in 50% of the patients [9].

Treatment of aHUS is based on supportive care together with C5 inhibitors (Eculizumab or Ravulizumab) [9]. About 75% of patients achieve hematologic normalization and preservation of renal function with this treatment [8].

Although malignant hemopathies can be related to TMA syndromes, the APL is not specifically described as a triggering cause of HUS. Only 3 cases of coexistence of these two pathologies have been published and they were not treated with complement-blocking drugs.

The objective of this report is to present a rare case of coexisting APL and aHUS successfully treated with Eculizumab that can be useful to the reader as a recognition pattern to identify similar cases in their own practices.

2. Case Presentation

2.1. Diagnostic of Acute Promyelocytic Leukemia

We report the case of a 48-years-old French woman that consulted the emer-

gency service addressing asthenia, bone pain, generalized ecchymosis, fever and metrorrhagia.

She had a history of papillary carcinoma thyroid at 43 years old (treated by thyroidectomy and Iratherapy, under hormonal supplementation with thyroxine), cholecystectomy, and presence of cysts in ovaries. The family history was negative for hematological diseases.

In the laboratory workup at admission a deep pancytopenia was observed with 7 g/dL of hemoglobin, 15.000 platelets/mm^3, and 3.000 WBC/mm^3 with 73% circulating blasts and 370 neutrophils/mm^3. Renal and hepatic function were preserved. The coagulation laboratories showed no alteration.

Myelogram and molecular biology studies were performed in which acute promyelocytic leukemia PML-RARα positive was diagnosed.

Due to the presence of a white blood cell count lower than 10,000/mm^3 and an age under 60 years old, the patient belongs to the standard risk group for relapse.

The patient started induction chemotherapy treatment based on ATRA and Idarubicin together with transfusion support.

After the induction treatment the patients achieved hematological and molecular complete response with normalization of hemoglobin and platelet count. She received two consolidation cycles with ATO, anthracyclines and cytarabine.

During the first consolidation cycle she presented peri-catheter axillary thrombosis treated with low molecular weight heparin.

2.2. Development of Thrombotic Microangiopathy and Initial Treatment

The patient began maintenance treatment with ATO, 6-mercaptopurine and methotrexate. Four weeks later she presented with clinical deterioration, vomiting and jaundice. Blood examination showed 10.3 g/dL of hemoglobin, 36.000/mm^3 platelets, 5700 WBC/mm^3, renal impairment (creatinine 133 μmol/L) and alteration of hepatogram (ASAT 96 UI/l, ALAT 107 UI/l) with a undetectable dosage of methotrexate.

24 hours after she had aggravation of the anemia (Hemoglobin 6.9 g/dL) and thrombopenia (platelets 4.000/mm^3), increased analytical parameters of hemolysis (undetectable haptoglobin and 2.5% of schistocytes) and progressive deterioration of renal function (creatinine 276 μmol/l) with preserved diuresis, without alteration of general hemostasis tests. No neurological symptoms were detected.

Considering the presence of signs compatible with TMA, the patient was transferred to the Intensive Care Unit and a determination of ADAMTS-13 activity was performed. Drug-related toxicity causes of TMA were ruled out, including methotrexate dosage which was negative. The Shiga toxin test was negative as well as HIV serology. There was no evidence of relapse of her APL as the PML-RARα was negative. She did not present clinical signs of bleeding.

The patient continued with progression of anemia (Hemoglobin 5.6 g/dL) and thrombocytopenia (1.000 platelets/mm^3) and creatinine increase, so she started

emergency treatment with daily plasma exchange plus corticotherapy. There was no significant improvement with this therapy.

The result of the ADAMTS13 enzyme activity dosage was 83% and the CH50 dosage was 16% (reference range 70% - 100%). The diagnosis of aHUS was made as other causes of TMA were ruled out.

The patient was transferred to a high complexity hospital where she started treatment with Eculizumab showing a clear clinical and analytical improvement, with initial recovery of blood count and renal function.

Complement system blockade was confirmed by Eculizumab dosing.

Antibacterial prophylactic treatment was performed with Oraciline and immunizations against encapsulated germs were applied.

However, the genetic study of the hereditary anomalies of the alternative complement pathway were negative (Factor H, MCP/CD46, Factor I, Factor B, C3, DGKE, CFHR and thrombomodulin) and there were no evidence of anti-factor H antibodies. Five months after the first application of the drug, the decision to discontinue treatment with Eculizumab was made.

2.3. Recurrence of Atypical Hemolytic Uremic Syndrome

After 4 months from discontinuation of Eculizumab, the patient presented a relapse of TMA with a severe renal involvement requiring hemodialysis. When the humanized monoclonal antibody against complement C5 treatment was restarted, the patient showed a favorable evolution with progressive normalization of blood count and improvement of renal function (creatinine 91 μmol/l) achieving the suspension of dialytic support.

The patient developed arterial hypertension that was controlled with a low dose of angiotensin-converting enzyme inhibitor.

Considering that the patient presented a recurrence with very severe renal involvement that responded favorably to treatment, the decision to continue with the treatment every 15 days was taken.

Despite the high risk of infections that patients under treatment with eculizumab have, the patient presented only recurrent episodes of urinary infection by *Escherichia coli* treated with oral antibiotic therapy and hygienic and dietary measures.

2.4. Evolution and Follow-Up

The patient resumed maintenance therapy for her leukemia 6 months after the aHUS and she occasionally required red blood cell transfusion due to anemia secondary to the toxicity of such treatment, with no signs suggestive of hemolysis.

She has been in complete molecular response for 3 years since le diagnosis of the APL. After 2.5 years since the diagnosis of aHUS, the patient continues under Eculizumab, maintains a creatinine 91 μmol/l, clearance of 64 ml/min; hemoglobin >14 g/dL and platelets >200,000/mm^3.

The patient remains under C5 inhibition and clinical-analytical controls,

without complications requiring hospitalization in relation to her treatment and pathology and with good quality of life.

3. Discussion

TMA is frequently associated with the malignant hemopathies, the treatments used (chemotherapies, bone marrow transplantation), and the associated complications (infections). In this setting, the diagnosis of aHUS is much less straightforward for patients with these comorbid conditions, are more difficult to handle, and require multidisciplinary work.

The diagnosis of aHUS relies on the absence of associated disease, no criteria for Shiga Toxin-HUS, and not meeting the criteria for thrombotic thrombocytopenic purpura (serum ADAMTS 13 activity <10% excludes the diagnosis of aHUS) [10]. TMA with comorbidities (eg. pre-existing nephropathy, autoimmune diseases, malignancy, hemopoietic stem cell transplantation) can exclude an aHUS diagnosis [7]. In the case presented the patient had a history of malignancy, however, APL is a disease that does not belong to the group of pathologies with a clear causal relationship to cause TMA. Moreover, the patient was in complete molecular remission of her leukemia at the time of manifesting the aHUS. Therefore, we do not consider it to be a case of TMA secondary to this patient's APL.

Ruling out pharmacological causes of TMA requires multidisciplinary work together with the pharmacovigilance team. In the presented case, the causal relationship with methotrexate was ruled out since the methotrexate dosage was negative at the time of the development of aHUS. All other chemotherapies that the patient was receiving (Mercaptopurine and ATRA) do not appear to be associated in the literature with the occurrence of HUS.

Our review of the literature identifies 3 reported cases of coexistence of APL and suspected aHUS. Candoni *et al.* reported in 2004 a case of a 68-years-old woman with clinical findings compatible with aHUS during induction therapy in which the patients died 5 weeks after the diagnosis [11]. Breccia *et al.* presented a case of a 47-years-old man with APL and a retinoic acid syndrome mimicking the haemolytic uremic syndrome during induction therapy [12]. Polania-Rusiilo *et al.* published in 2013 the case of a 37-years-old man with a TMA at the time of diagnosis of APL who developed renal cortical necrosis [13]. These published cases did not report the performance of genetic studies or dosage of ADAMTS13 activity to rule out other causes of TMA. To the best of our knowledge, this is the first published case of the presentation in a patient with a PML under maintenance treatment successfully treated with Eculizumab.

Multicenter studies are required to assess whether there is a causal relationship between these two pathologies or whether this is a random isolated case.

The patient presented had a negative test for mutations that causes dysregulation of the complement alternative pathway, but these alterations are detected only in 40% - 60% of patients with aHUS [14] as presently available laboratory tests do not identify all patients with defective complement regulation.

Therapeutic terminal complement blockade at the level of C5 with Eculizumab changed the natural history of complement mediated HUS, reducing the percentage of mortality or acquired end-stage renal disease within 1 year of diagnosis from 50% to 15%. The clinical improvement is usually observed in the first weeks after C5 inhibition, achieving a complete or near complete response after 3 to 6 months of therapy [9].

The adult treatment protocol consists of four weekly 900 mg doses, followed by a maintenance 1200 mg doses every two weeks. There is no consensus on the duration of therapy [15]. The literature published support the practice of early Eculizumab initiation and a trial of cessation with regular monitoring when patients achieve clinical remission. In case of recurrence, restarting terminal complement inhibition is the most cost-effective treatment as it permits recovered renal function in virtually all patients [9] [15]. Our patient presented a relapse of aHUS after discontinuation of treatment and the response to the restart of treatment was satisfactory, allowing her to complete the treatment of her APL.

There is no previously published literature on the use of Eculizumab in patients with aHUS presenting simultaneously with APL. The question of whether this is a concomitant coincidental presentation or a causal relationship between the two pathologies cannot be answered. The presented case could serve as an example of therapeutic management for future similar cases, although controlled clinical trials are required to establish recommendations based on solid clinical evidence.

4. Conclusions

The importance of the presented case lies in the coexistence of two rare and severe hematologic pathologies (LPA and aHUS), with similar clinical presentations but with different molecular bases.

This is the first published case in which a successful treatment of aHUS with Eculizumab is performed in the context of a patient undergoing chemotherapy treatment for APL.

Studies are needed to evaluate the relationship between these two diseases in order to achieve a better understanding of their biology and to optimize the therapeutic management of complex cases such as the one presented.

Informed Consent

The patient's oral consent was obtained for the publication of this case.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Coronary Artery Bypass with Myxedema

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Abstract

Introduction Hypothyroidism increases the risk of cardiovascular complications in patients scheduled for coronary artery bypass grafting. Atrial fibrillation is one of its cardiac complications. Case Report Our 45-year-old male patient was admitted to the Emergency Medicine Clinic of our hospital with chest pain that started in the left arm and extended to the chin 2 days ago. It was noted that the patient had hypothyroidism, but did not have any medication for the disease. On physical examination, dry and pale skin, sparse coarse hair, non-pitting edema were diagnosed with acute coronary artery disease. No signs of ischemia were observed on the ECG at the time of admission, but bradycardic sinus rhythm was recorded. The patient was started to be followed up with the diagnosis of NON-ST myocardial infarction. Nitroglycerin 0.25 - 2 mcgr/h and morphine 2 mg were administered intravenously to the patient whose anginal complaints continued after admission. Anginal complaint continued was operated in 1:1 mode by attaching an intraaortic balloon pump (Maquet Sensation 7Fr 40 cc, Datascope CS300 console) via the left femoral artery. Surgery procedure: The patient was performed with median sternotomi (aortic, two-stage cannulation). While the patient was cooled to 32 degrees and given blood cardioplegia (St. Thomas II) and applied topical cold. After distal anastomoses were performed with saphenous vein graft. Total cross-clamp time was 60 min. Epinephrine was given for bradycardia sinus rhythm. No cardiovascular complications were encountered while being followed in the intensive care unit. The patient was discharged on the 6th postoperative day. Conlucion: Our case, who was taken to emergency CABG operation with myxedema, was discharged without any cardiovascular, respiratory or metabolic complications both in the perioperative and postoperative periods. In this case, the major stress caused by cardiovascular surgery was successfully overcome by both the cardiovascular surgery team and the anesthesiology team.

Keywords

Hypothyroidism, Cabg, Myxedema, Atrial Fibrillation

1. Introduction

Thyroid hormones have a complementary role in cardiac and peripheral vascular functions. They show a positive inotropic effect, especially by increasing the heart rate through β1 adrenergic receptors. In addition, increased preload causes an increase in stroke volume as a result of decreased afterload. Increased stroke volume leads to increased cardiac output [1] [2] [3] [4]. Atrial fibrillation is an expected cardiac complication in hypothyroid patients. In these patients, a picture similar to decompensated heart failure can be seen due to the imbalance in thyroid hormones arising from the hypothalamic-pituitary axis [5]. Hypothyroidism increases the risk of cardiovascular complications in patients scheduled for coronary artery bypass grafting. Especially postoperative atrial fibrillation is one of its known complications [6].

2. Case Report

Our 45-year-old male patient was admitted to the Emergency Medicine Clinic of our hospital with chest pain that started in the left arm and extended to the chin 2 days ago. It was noted that the patient had hypothyroidism, but did not have any medication for the disease. In recent months, it has been reported that weight gain and excessive dryness of the skin have developed. On physical examination, dry and pale skin, sparse coarse hair, non-pitting edema were diagnosed with acute coronary artery disease, and electrocardiography (ECG) (Picture 1) was taken and a sample was sent to the laboratory to evaluate biochemical parameters. No signs of ischemia were observed on the ECG at the time of admission, but bradycardic sinus rhythm was recorded (**Figure 1(a)**). Changes in cardiac enzymes in laboratory parameters (Troponin T: 1294 ng/l (reference range: 0 - 12) Creatinine Kinase (CK): 412 U/L (reference range: 0 - 171) Lactate Dehydrogenase (LDH): 346 U/L (reference range: 135 - 225)) accompanying Thyroid Stimulating Hormone (TSH) elevation (>100 IU/ml reference range: 0.27 - 4.2) Free T3 (1.42 ng/dL reference range: 2 - 4.2)-Free T4 (0.26 ng/dL reference range: 0.93 - 1.7) was recorded. The laboratory data of the case are shown in **Table 1**. The patient was started to be followed up in the coronary intensive care unit with the diagnosis of NON-ST myocardial infarction. In transthoracic echocardiography, LV EF: 60%, LVES: 31 mm LVED: 44 mm IVS: 10 mm Posterior wall: 9 mm Left atrium: 30 mm Aortic root: 19 mm. Coronary artery angiography showed LMCA 90% stenosis, LAD osteal 80% stenosis, LAD mid 80% stenosis, thin plaque in LAD after D1, CX with plaque, RCA with nondominant plaque. Coronary artery bypass grafting (CABG) operation was decided due to the critical left main coronary artery lesion of the case and the presence of

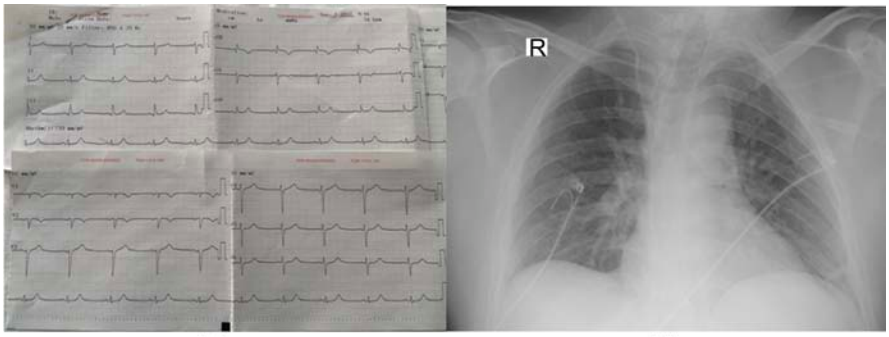

Figure 1. (a) Electrocardiogram 1. (b) Chest X-ray on admission.

Table 1. Laboratory parameters of the case.

	Admission	Preoperative	Before Discharge
TSH	>100 µIU/ml	>100 µIU/ml	>100 µIU/ml
Free T_3	1.42 ng/dL	1.29 ng/dL	1.59 ng/dL
Free T_4	0.26 ng/dL	0.24 ng/dL	1.21 ng/dL
TpnT	758.3 ng/dL	927 ng/dL	250 ng/dL
CK	255 UI/L	246 UI/L	146 UI/L
LDH	336 UI/L	334 UI/L	200 UI/L
Glucose	100.2 mg/dL	107.7 mg/dL	116.3 mg/dL
Creatinin	1.03 mg/dL	0.8 mg/dL	0.82 mg/dL
BUN	87	108	107
AST	90 U/L	61.1 U/L	30.8 U/L

consecutive lesions that cause severe stenosis in the LAD. CABG preparation was started for the patient who was taken to the cardiovascular surgery intensive care unit. Nitroglycerin 0.25 - 2 mcgr/h and morphine 2 mg was administered intravenously to the patient whose anginal complaints continued after he was admitted to the intensive care unit, and the angina pectoris of the patient was tried to be controlled. However, the patient whose anginal complaint continued was operated in 1:1 mode by attaching an intraaortic balloon pump (Maquet Sensation® 7Fr 40 cc – Datascope CS300 console) via the left femoral artery. Due to the high TSH level in the preoperative preparation, LT4 was added to the treatment with endocrinologist consultation. The laboratory values of the case are shown in Table 1. Urgent CABG decision was taken when angina pectoris and Troponin T had a decreasing trend (758 ng/dl) and increased again (927 ng/dl), and systolic arterial pressure decreased below 90 mmHg.

In the preoperative anesthesia examination, angina pectoris continued, coarse brittle hair, dry skin, edema around the mouth, swelling in the tongue, and non-pitting edema were observed on the skin. It has been evaluated for difficult intubation but, difficult intubation has not been predicted. No pathology was detected in lung sounds and X-ray (Figure 1(b)). No pericardial or pleural effusion was found on chest X-ray. However, in the preoperative ECG, it was ob-

served that the patient was bradycardic (Figure 1(a)). During the surgical procedure: Hydrocortisol 50 mg every 8 hours was added to LT4 treatment in preoperative edema in order to prevent relative hypocortisolenemia due to major stress that may occur during the surgical procedure. No hypoglycemia was observed in the case. American Society of Anesthesiology (ASA) 3E was given until emergency operation. The patient was operated on the 3rd day of hospitalization and induction was performed with midazolam 10 mg, fentanyl 350 mcgr, and rocuronium 40 mg. The patient whose airway was secured by orotracheal intubation (Drager Perseus ®A 500 anesthesia workstations) was administered remifentanil 0.01 mcgr/kg/min, Deflurane 4% for maintenance of anesthesia. Standard monitoring was applied in the CABG procedure. In the pre-induction hemodynamic monitoring, peak heart rate 60/min arterial pressure was recorded as 105/60 mmHg CVP: 4 mmHg. Follow-up arterial blood gas of the case is shown in Table 2. In the perioperative period, anesthesia was maintained with a CVP of 4 - 6 mmHg and a mean arterial pressure of 65 - 75 mmHg.

Surgical Procedure:

After median sternotomy under general anesthesia, left internal mammarian artery and saphenous vein were prepared as grafts. After the pericardium was opened, it was suspended and aortic arterial and right atrial two-stage venous cannulation followed by cardiopulmonary bypass (CPB). While the patient was cooled to 32 degrees, cannulation was completed by placing a root cannula in the ascending aorta. When the cooling was completed, the heart was arrested in diastole by placing a cross-clamp on the aorta, giving blood cardioplegia (St. Thomas II) through the aortic root cannula and applying topical cold. After RCA and CX distal anastomoses were performed with saphenous vein graft, the patient was started to be warmed while performing the LIMA-LAD anastomosis. After the distal anastomoses were completed, the cross clamp was removed. Total cross-clamp time was 60 min. Cross started to work with sinus rhythm after clamping. After the proximal anastomoses of the saphenous vein grafts were completed by placing a side clamp on the ascending aorta, the patient was removed from the pump and decannulated. Epinephrine 0.01 mcg/kg/min infusion

Table 2. Peroperative arterial blood gas samples.

	pH	PCO_2	PO_2	%Hct	Hgb	P	Na	Ca	Gl	Lac	BE
After induction	7.42	35.2	173	40.9	13.3	3.6	139	1.11	98	0.5	−0.9
Before pomp	7.44	32.1	129	36.4	11.8	4.1	138	1.24	96	0.6	−1.0
After cross klemp	7.40	38.1	277	24.2	7.8	4.5	139	1.16	119	1.1	−0.7
After pomp	7.38	38.4	303	25.1	8.0	4.6	138	1.26	138	1.2	−1.8
End of surgergy	7.36	37.5	111	26.9	8.7	3.9	142	1.21	156	1.7	−3.8

Abbreviations: Hct: Hematocrit Hgb: Hemoglobin P: Potassium Na: Sodium Ca: Calsium Gl: Glucose Lac: Lactat BE: Base Deficit.

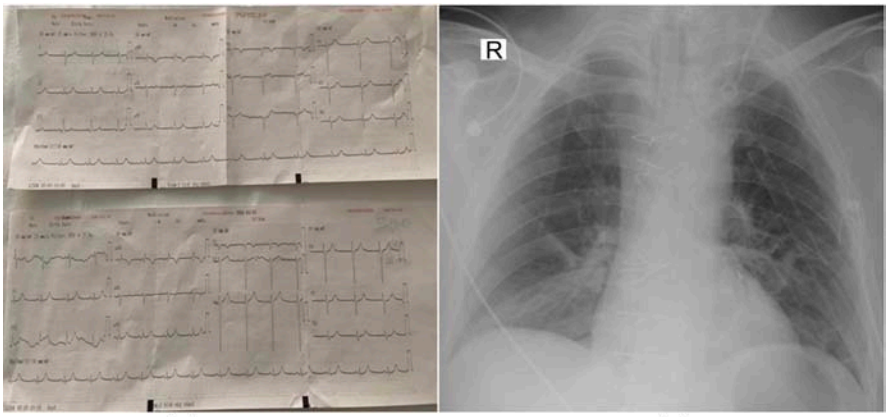

Figure 2. (a) Electrocardiogram; (b) Postoperative chest X-ray.

was added in order to have a positive chronotropic-inotropic effect in bradycardia sinus rhythm that continued after pump discharge. CABG procedure was performed by 3 cardiovascular surgeons (Dr. ST, Dr. YK, Dr. HT). The patient, who was extubated in the 5th postoperative hour without any problems, was taken to the service on the 2nd day of follow-up and treatment in the intensive care unit. LT4 and hydrocortisone were continued in the postoperative treatment. Hydrocortisone was discontinued on the 2nd postoperative day. No cardiovascular complications were encountered while being followed in the intensive care unit. The patient was discharged to his healthy home on the 6th postoperative day. Postoperative ECG and X-ray were shown in **Figure 2**.

3. Discussion and Conclusions

The effects of thyroid hormones on the cardiovascular system are known. Especially in hypothyroid cases, myocardial ischemia and vascular pathologies are more common due to endothelial dysfunction [7]-[11]. Endothelial dysfunction may cause bleeding during hemostasis. However, in our case, no problem was observed in bleeding diathesis during the whole process. Increased vascular resistance may cause difficulties in hemodynamic stability in CABG surgery. After a surgery performed for hypothyroidism, atrial fibrillation is one of the known comorbidities [12]. Lack of adequate T3 hormone concentration in the plasma, results in a decrease in the level of calcium ions in the intracellular environment [13]. The decrease in Free T3 in the postoperative period has been reported as an independent risk factor for atrial fibrillation after CABG surgery was performed [14]. On the contrary, our case was bradycardic and required positive chronotropic agent support in the perioperative period. Contrary to the literature, the dominance of bardycardic sinus rhythm was noted in the postoperative period. In the literature, no clear results can be obtained in studies on hypothyroid cases. In a randomized prospective study of 142 people, it was observed that T3 hormone replacement increased cardiac output while systemic vascular resistance was decreasing. A prospective randomized study of 170 people used high cardiac index

and low inotropic support after CABG [15]. In another randomized controlled study, the use of dopamine, saline, and T3 did not have any effect on hemodynamics or inotropic support [16]. In our case, low-dose adrenaline infusion was needed due to bradycardia and hypotension. The bradycardic picture supports myxedema. The inability to perform invasive hemodynamic monitoring is a limitation of the study. While hypertension is expected in severe hypothyroidism, hypotension secondary to myarcardial ischemia and labile hemodynamics were observed in our case. While emergency CABG was planned due to anginal pain being unresponsive to medical treatment and increased myocardial ischemia, hemodynamic stability was provided with an intra-aortic balloon pump. Although there was edema around the mouth and tongue in our case, no problems were encountered during orotracheal intubation. No pleural fluid or pulmonary edema was observed. No respiratory pathology was encountered in the oxygenation of the patient. In the emergency operation, grafting was applied to three coronary arteries, and the peroperative process was completed without any problems.

Postoperative hypothyroidism processes vary due to co-morbidities and possible complications. Values ranging from 9 to 13 days have been reported [17]. Our case was discharged on the 5th postoperative day with recovery.

In summary, Our case, who was taken to emergency CABG operation with myxedema, was discharged without any cardiovascular, respiratory or metabolic complications both in the perioperative and postoperative periods. In this case, the major stress caused by cardiovascular surgery was successfully overcome by both the cardiovascular surgery team and the anesthesiology team.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

TSH: Thyroid Stimulating
ECG: Electrocardiography
CABG: Coroner Artery Bypass Grefting
CPB: Cardiopulmonery Bypass
AO: Aort
LAD: Left Anterior Desencing
LMCA: Left Mean Coronary Artery
LIMA: Leftinternal Mammarian Artery
CX: Circumflex Artery
CVP: Central Venous Pressure
ASA: American Society of Anaesthesia
CK: Creatinin Creatinin
LDH: Lactate Dehydrogenase

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Osteogenesis Imperfecta: One Disease, Two or More Faces: A Case Report

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Abstract

Being such a rare condition in paediatrics, osteogenesis imperfecta (OI) is not a diagnosis which is made often. It is however, a diagnosis necessitating early diagnosis and timeous and effective management to improve morbidity and increase the quality of life for our patients. We report two cases of osteogenesis imperfecta in this case report to highlight the different phenotypic presentations. Both of these patients are unique in their presentations and each case highlights the importance of a high clinical index of suspicion by the practitioner in making the diagnosis of osteogenesis imperfecta. The first case is a patient who was diagnosed with osteogenesis imperfecta on day one of life. She had disproportionate short stature, blue sclera, a small chest and bowing of her lower limbs with swellings and tenderness over both of her femurs. A babygram radiograph revealed multiple fractures, with the presence of callus formation at some fracture sites suggesting intrauterine fractures. The second case is a patient who had normal anthropometry and was well at birth. She was subsequently diagnosed at two weeks of age when she presented to the Chris Hani Baragwanath Academic Hospital with an *E. coli* meningitis and she was suspected to have a right clavicular fracture and possibly rib fractures as she had pain on palpation over these areas. She was noted to have no blue sclera. Subsequent X-rays confirmed a right clavicular fracture as well as left and right rib fractures at different stages of healing. A lateral skull radiograph revealed Wormian bones. With no available genetic testing in South Africa, both diagnoses were made clinically. Both of our patients were started on zoledronic acid at three months of age and were followed up by the Metabolic Unit at the Chis Hani Baragwanath Academic Hospital. This case report of two patients highlights the characteristics important in diagnosing and treating this uncommon condition with varying phenotypical presentations, thus ensuring that the diagnosis is not missed or misdiagnosed: one disorder, two different faces.

Keywords

Paediatrics, Osteogenesis Imperfecta, Case Report, Fractures, South Africa

1. Introduction

Osteogenesis imperfecta is a rare genetic disorder with a global incidence of one per 20,000 live births [1]. Interestingly, the proportion of *de novo* mutations, which is 35% - 60%, is lower than that of other musculoskeletal disorders [1]. While the incidence is unknown, research shows that Type III osteogenesis imperfecta occurs in the indigenous black population of South Africa, with a minimum population frequency of 0.6 per 100,000 [2]. In a study by Oduah *et al*., which was based at the Chris Hani Baragwanath Academic Hospital, it was found that 48.7% of the patients presenting to the Metabolic Bone clinic had type III osteogenesis imperfecta; with the next most prevalent being type IV, comprising 29.5% of the patients in this study [3]. Type III osteogenesis imperfecta is referred to as "progressively deforming" which emphasises its severity. The pattern of inheritance of type III osteogenesis imperfecta is either autosomal recessive or autosomal dominant, with the former being more prevalent in South Africa [2].

There are 18 gene-based types of osteogenesis imperfecta [4]. With genetic testing not being readily available for routine analysis, especially in our state hospitals, we rely greatly on clinical and radiological features to characterize the type of osteogenesis imperfecta. Identification of specific genes would further assist in accurately classifying osteogenesis imperfecta according to type, which is important in prognostication. As a broad clinical and radiological classification, the Sillence phenotypic classification classifies Type I osteogenesis imperfecta as mild, type II as severe and perinatally lethal, type III as severely deforming and type IV as moderately deforming [4].

Dominant mutations in the COL1A1 (collagen type 1 alpha-1 chain) and COL1A2 (collagen type 1 alpha-2 chain) gene encompass the majority of osteogenesis imperfecta cases [5]. It has been found that these genes are involved in 90% of cases of osteogenesis imperfecta [6]. These mutations result in a decreased production or abnormal synthesis of collagen. There are however, 17 other genes involved in collagen synthesis or osteoblast formation which are also implicated in osteogenesis imperfecta [7].

Mutations of a variety of genes result in Type III osteogenesis imperfecta, with mutations in the FKBP10 gene being reported in South Africa [2]. In the study by Vorster *et al*., 45% of patients with osteogenesis imperfecta Type III had mutations in the FKBP10 gene [2]. The study emphasized the necessity of genetic testing for families of patients with osteogenesis imperfecta as this could assist with carrier detection, antenatal diagnosis and preimplantation genetic diagnosis. However, Zhytnik *et al*. demonstrated that 85.29% of osteogenesis imperfecta

Type III patients in their study had de novo mutations [1].

This case report describes two interesting cases of patients with differing forms of osteogenesis imperfecta. Informed consent was obtained for both patients. The objective of this case report is to bring awareness to osteogenesis imperfecta and the importance of early diagnosis and referral to decrease morbidity and ensure prompt management and support.

2. Case Report

Case 1 was a baby girl born at Chris Hani Baragwanath Academic Hospital via spontaneous vaginal delivery. She was born premature at 34 weeks gestation with a birthweight of 1185 g, a length of 34 cm and a head circumference of 24 cm. All of her growth parameters plotted below −2 standard deviations on gestation-appropriate growth charts. She had an upper to lower segment ratio of 1.3:1 indicating disproportionate short stature. Clinically, she had a soft skull with mild sutural diastasis and was noted to have blue sclera. She had a small chest with mild subcostal recessions but clinically normal breath sounds auscultated bilaterally. Her cardiovascular examination was normal, as were her abdominal, genitourinary and neurological examinations. There was no increased laxity of her ligaments or skin. On mild palpation of the long bones, there were swellings and tenderness felt over both her femurs with bowing of her lower limbs. There were no other skeletal abnormalities noted of the upper limbs and she had no scoliosis. Her respiratory distress settled on nasal prong oxygen.

A clinical diagnosis of skeletal dysplasia was made and she was admitted to the neonatal unit for further workup and management. A babygram radiograph revealed six fractures involving her right clavicle, humerus, femur and tibia and her left ulnar and femur (**Figure 1**). The presence of callus formation at some of the fracture sites suggested intrauterine fractures. Her bones appeared to be osteopenic. There was no family history of any skeletal dysplasias. Blood investigations were unremarkable and her congenital pneumonia resolved within four days after treatment with intravenous antibiotics. Cranial ultrasound at two weeks of age was normal and ruled out hydrocephalus at this stage. She grew well in the ward to a discharge weight of two kilograms and by this time her mother had gained confidence in handling her and was comfortable to take her home.

Case 2 was a baby born at term with a birth weight of 2670 g and a length of 49 cm which plotted appropriately for gestational age. There was no family history of any medical conditions or comorbidities. There were no obvious skeletalfeatures recognized at birth and a paediatric review was not requested as she was well at delivery and required no hospital admission. Thereafter, at two weeks of age, she presented to Chris Hani Baragwanath Academic Hospital and was diagnosed with an *E. coli* meningitis. She was noted to have blue sclera and she appeared to be in pain on handling during the admission. The pain was particularly over her right clavicle and rib cage. Radiographs evidenced fractures of the right clavicle and right and left ribs at different stages of healing (**Figure 2**). A

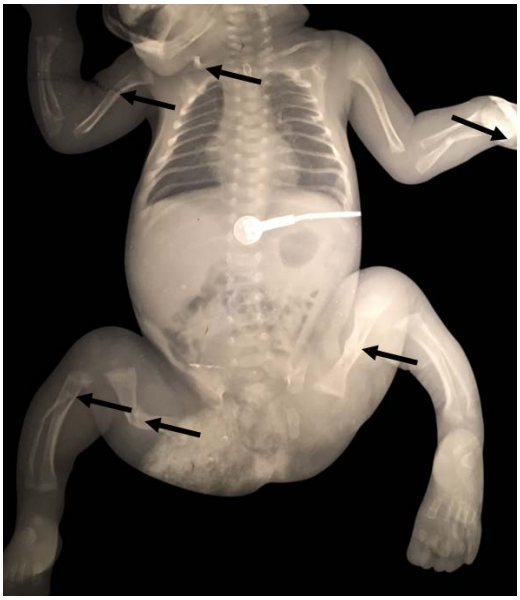

Figure 1. Is a babygram of the patient from Case 1 showing six fractures as denoted by the arrows.

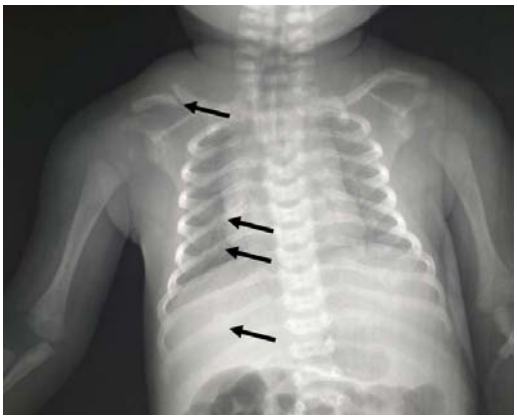

Figure 2. Shows the right clavicular and rib fractures (as demonstrated by the arrows) found in the patient for Case 2. These fractures were noted to be in different stages of healing. The bones also appear oste.

lateral skull radiograph revealed Wormian bones (**Figure 3**).

The severe type of osteogenesis imperfecta (Case 1) presented at birth with clinical features of OI, fractures and deformities whilst the possible moderate type (Case 2) with blue sclera had presented at two weeks of age at a tertiary institution with an underlying meningitis, and with the experience of the paediatricians and bone specialists was diagnosed at this stage with OI. If the child was not admitted, she would have possibly been a delayed diagnosis as the pain or crying may have been attributed to other causes such as colic and the fractures could have been missed.

Case 1 was admitted for a lower respiratory tract infection two weeks after

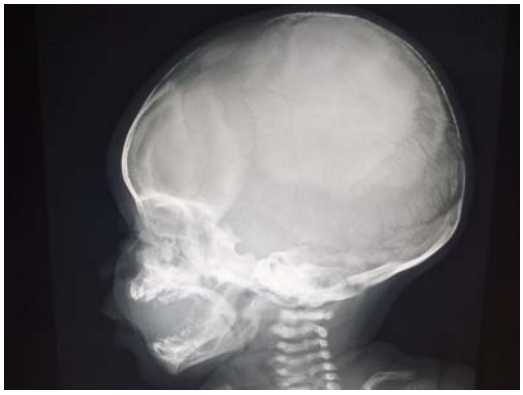

Figure 3. Clearly demonstrates the presence of Wormian bones on this lateral skull Xray of the patient in Case 2.

discharge and unfortunately deteriorated and demised in the paediatric ward. Case 2 is doing well. She follows up with the Paediatric Metabolic Bone clinic and receives bisphosphonates.

3. Discussion

In South Africa, the diagnosis of OI is largely a clinical and radiological diagnosis together with the history of fragility fractures. Case 1 was diagnosed as Type III osteogenesis imperfecta which is associated with long term survival, despite the multiple in utero fractures, multiple long bone and rib fractures at birth and limb deformities [8]. Case 2 was diagnosed as a possible Type IV osteogenesis imperfecta, a comparatively less severe form of osteogenesis imperfecta with a later diagnosis. Radiologically, fractures in various stages of healing were noted, as well as Wormian bones on skull Xray. Short stature with blue sclera also pointed to the diagnosis of Type IV osteogenesis imperfecta.

Clinical and radiographic features, family history and natural history classifies osteogenesis imperfecta into four main types [9]. This is broadened to 18 types with the addition of genetic assessment and the identification of the specific genes involved [9]. Importantly to note is that clinical and radiological features overlap across the various types. Classic non-deforming osteogenesis imperfecta (type I OI), is characterized by normal stature and blue sclera [9]. Fractures in this group of patients usually first occur with walking and falling, with a few to several fractures per year which subsequently decrease in frequency after puberty [9]. A subset of osteogenesis type I is dentinogenesis imperfecta (OI type IB) when there is premature wearing down of the teeth [9].

Perinatally lethal osteogenesis imperfecta (type II OI) is apparent at birth with dark blue sclera, extremely fragile connective tissue, a large soft skull and short and bowed extremities [9]. Affected infants occasionally demise in utero, with majority demising in the immediate perinatal period – 80% within the first week of life, usually resulting from pulmonary insufficiency related to small thoraces, rib fractures or flail chests with unstable ribs [9].

Progressively deforming osteogenesis imperfecta (type III OI) is apparent at birth with fractures in the neonatal period and blue sclera [9]. Patients have short stature and because of severe bone fragility and marked bone deformity, they require assistance for mobilizing and usually require a wheelchair [9]. Patients may develop dentinogenesis imperfecta and some patients have a relative macrocephaly and barrel chest deformity [9]. Basilar impression can occur and progress to brain stem compression, obstructive hydrocephalus and syringomyelia [9]. Commonly variable osteogenesis imperfecta (type IV OI) is characterized by mild short stature, dentinogenesis imperfecta and blue sclera in the neonatal period which change to grey later on [9]. Hearing loss my occur in adulthood and in some patients basilar impression can occur [9].

Of note, blue sclera are also present in other conditions such as Ehler-Danlos, Russel-Silver, Marshall-Smith, Loeys-Dietz and De Barsy syndromes, as well as in some patients with iron deficiency [7]. Wormian bones can be present in the normal paediatric population as well as conditions such as hypophosphatasia, hydrocephalus, congenital hypothyroidism and Down Syndrome [7]. Various other conditions increase the risk of fractures and these also need to be considered as differential diagnoses. These include metabolic bone disease of prematurity, idiopathic juvenile osteoporosis or monogenetic osteoporosis, Ehlers-Danlos syndrome, hypophosphatasia, hereditary hyperphosphatasia, osteoporosis-pseudoglioma and vitamin D and/or calcium deficiency rickets [7]. This shows the importance of a holistic assessment of patients when making a clinical diagnosis.

It is also important to consider other syndromes which may resemble osteogenesis imperfecta. Cole-Carpenter Syndrome patients have brittle bones with craniosynostosis and ocular proptosis [10]. Bruck syndrome is a disorder with brittle bones and congenital joint contractures [10]. Osteoporosis pseudoglioma syndrome patients have mild to moderate osteogenesis imperfecta and blindness due to secondary glaucoma [10]. Other conditions with brittle bones have associated redundant callus formation, mineralization defects or rhizomelia [10]. This highlights the importance of genetic testing to confirm a diagnosis of osteogenesis imperfecta and rule out other conditions with similar clinical findings.

Radiological evidence of fractures helps with diagnosis of osteogenesis imperfecta. Typical radiographic features include Wormian bones on lateral skull radiographs, which are small supernumerary bones found between the sutures and fontanelles of the skull [7]. They are suggestive of osteogenesis imperfecta and are occasionally evident in type I, III and IV [9]. Other radiological features include fractures at various stages of healing and spinal compression fractures or "codfish vertebrae" which are more commonly seen in adult patients [9]. Protrusio acetabuli, whereby the acetabulum bulges into the pelvic cavity, is occasionally seen in patients with type IV osteogenesis imperfecta [9]. Thin cortices of the extremity bones occurs in types I, III and IV versus the severely deformed, broad, crumpled and bent femurs found in patients with type II osteogenesis imperfecta [9]. Small beaded ribs are pathognomonic of type II, versus thin ribs being observed in patients with type III osteogenesis imperfecta [9].

In terms of laboratory findings, vitamin D, calcium, phosphorous and alkaline phosphatase are typically normal with an occasional raise in alkaline phosphatase post fractures [9]. Markers of bone resorption (C-telopeptide of type 1 collagen) may be higher and markers of bone formation (C-terminal propeptide of type 1 procollagen) may be lower in patients with osteogenesis imperfecta, especially in severely affected patients [11].

Prompt diagnosis of osteogenesis imperfecta is important to prevent further complications. Management of this condition is multidisciplinary and involves paediatricians, endocrinologists, geneticists, orthopaedic surgeons, dentists, social workers, psychologists, physiotherapists and occupational therapists. The aim is to improve and maximize function and thus outcomes [8]. The mainstay of treatment for osteogenesis imperfecta is bisphosphonates, which has been shown to decrease bone turnover, bone pain, improve bone mineral density and reduce fracture rates [12].

Besides fractures, chronic pain (irrespective of the type of osteogenesis imperfecta) even without fractures is a major cause of morbidity in patients with osteogenesis imperfecta. The pathophysiology of this chronic pain is unclear but it is speculated that inflammatory cytokines, such as prostaglandins and thromboxanes, may contribute to bone turnover and result in pain [12]. The pain may subsequently result in delayed motor development. This highlights the importance of treatment in decreasing morbidity and maximizing functional capabilities. Bisphosphonates is important in pain control in patients with osteogenesis imperfecta.

Both of our patients were started on zoledronic acid at three months of age. Studies have shown that zoledronic acid has a longer biological half-life (thus allowing for longer dosing intervals) and can also be given more rapidly as a half hour infusion [8]. Comparing with pamidronate, zoledronic acid has a similar response in terms of reported quality of life and bone density [8]. A study by Garganta, *et al*. showed an acute reduction of pain and improved daily functioning in patients with chronic cyclic treatment of a half hour infusion of zoledronic acid at 6 monthly intervals [12]. Pain improved immediately after the infusion and analgesia lasted for several weeks and subsequently waned [12]. It was demonstrated that pain and functional levels return to pre-treatment levels by the subsequent infusion [12].

An important modality in treatment along with bisphosphonates is orthopaedic interventions such as intramedullary telescopic rods which significantly improve patient mobility [8]. Important to consider here is the timing of bisphosphonate therapy after intramedullary rod insertion as callus formation at the osteotomy site needs to occur [8]. It has been shown that bisphosphonate therapy delays the healing of osteotomy sites after intramedullary rod insertion [13]. A study by Anam *et al*. showed that delayed osteotomy healing was significantly lower with a bisphosphonate infusion-free interval of four months post osteotomy and with a change in surgical method, an osteotome was used instead of an oscillating power saw [13]. Unfortunately, they were unable to identify the effects of each contribut-

ing factor individually [13]. The same approach of temporarily stopping bisphosphonates applies when patients sustain a fracture to allow for healing. Orthopaedic management is also required for the treatment of scoliosis [8].

An often overlooked, yet extremely important, aspect in the management of children with osteogenesis imperfecta is the psychological care of our patients and their families. Osteogenesis imperfecta can be an overwhelming experience for patients and their families. It is important to consider the psychosocial implications at various developmental stages of childhood and adolescence [8]. For Case 1, who was diagnosed on day one of life, the diagnosis came as a surprise for her mother, who had never heard of such a condition before. She was scared to even handle her baby initially as she cried from pain with minimal movements, despite analgesia. Over time, she gained confidence as she became more comfortable with handling her.

An article by Stephen *et al*. highlights the psychosocial challenges of osteogenesis imperfecta Type III in South Africa [14]. Parents had initial feelings of shock, depression and anxiety as they now had a child with a physical disability [14]. These feelings then progressed to helplessness, loneliness and stress with unexpected financial implications [14]. Adequate emotional and psychological support greatly improves parents' feelings and their outlook on the condition osteogenesis imperfecta. Parents then become more involved with the realization of the importance of providing support for their children. There are available support groups for patients with osteogenesis imperfecta and their families in South Africa which offer emotional as well as financial support where possible.

Children affected with osteogenesis imperfecta also need to deal with physical and emotional barriers that come with the diagnosis [14]. The use of adaptive devices allow for full independence which in turn benefits patients psychologically [14]. The physical barriers that children with osteogenesis imperfecta face at school which limit mobility also need to be addressed [14]. As this is an evolving condition with differing implications throughout a child's life, great care and consideration needs to be taken at every step of the way.

4. Conclusion

This case report aimed to highlight the importance of consideration and early diagnosis of this rare yet prevalent condition. Timeous and effective management, in addition to the importance of a holistic approach, in order to decrease morbidity and increase the quality of life for our patients with osteogenesis imperfecta is mandatory.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Treatment and Maintenance of Interstitial Cystitis/Bladder Pain Syndrome in Female Patients with Cetirizine-Famotidine: A Case Series

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Abstract

Purpose: Interstitial cystitis/Bladder pain syndrome is an inflammatory disorder of the bladder, for which histamine has been implicated in the pathogenesis of the disease. The condition is often refractory to standard-of-care medical treatments, including the antihistamines hydroxyzine or cimetidine, and procedures. Herein we report a physician-sponsored proof-of-principle case series of four adult female patients with chronic painful bladder and frequent urination, who were treated once daily with a low dose H1 + H2 histamine receptor antagonist combination. Materials and Methods: Four adult females with Interstitial cystitis/Bladder pain syndrome were treated once daily with a compounded oral dosage form containing the H1 receptor antagonist-cetirizine 8 mg in combination with the H2 receptor antagonist-famotidine 22 mg. The case series consists of a retrospective review of the symptom severity prior to versus following H1 + H2 treatment. Results and Conclusions: The once daily dual histamine receptor antagonist therapy substantially reduced the pain and urination frequency, and prophylactically maintained all four patients long-term with substantially reduced disease severity. The reduction in symptom severity was achieved at amounts that do not exceed the US FDA approved and exceptionally safe daily doses for the two over-the-counter monotherapies. This case series provides proof-of-principle evidence that a dual antihistamine combination of cetirizine plus famotidine effectively treated and maintained female patients, who were previously refractory to standard-of-care medications and/or procedures.

Keywords

Histamine, Antihistamine, Bladder, Treatment, Prophylaxis

1. Introduction

Interstitial cystitis/Bladder pain syndrome (IC/BPS) is an inflammatory disorder of the bladder [1]. The primary clinical symptom of IC/BPS is chronic pain of the bladder (and/or pelvic region), and the disorder is sometimes termed as "painful bladder syndrome". Associated with the pain are increased frequency of urination when awake and/or while attempting to sleep (*i.e.*, nocturia), and/or urinary urgency. These symptoms and others (e.g., urinary incontinence, mental anxiety) associated with IC/BPS can result in substantial disruptions of normal activities, such as the abilities to work, exercise, sleep, concentrate, and to enjoy sexual intercourse. IC/BPS is a chronic painful bladder condition that is more common in women (*i.e.*, ca. 90 percent of cases). Diagnosis of IC/BPS can be problematic, as there are no specific tests to affirm a diagnosis. Beyond history, physical, and questionnaire data, physicians may use cystoscopy to examine the bladder for inflammation, Hunner lesions, and functional capacity while excluding other etiologies such as foreign bodies, stones, or malignancy.

Initial therapies for IC/BPS have included behavioral changes, physical therapy, and over-the-counter medications, such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and phenazopyridine. Prescription medication options include the tricyclic antidepressant, amitriptyline. Additionally, medications aimed at histamine action or release, such as H1 or H2 receptor antagonists (hydroxyzine or cimetidine, respectively) or pentosan polysulfate are common starting points [1] [2]. Multimodal therapy has been proposed to be more effective than monotherapies in the treatment of IC/BPS [3]. In spite of the multiple available standard-of-care (SOC) medications and procedures, many patients' symptoms remain refractory to treatment for years. Thus, there remains a need for a safe and effective treatment and/or prophylaxis for IC/BPS or the symptoms thereof.

Histamine has been strongly implicated in the pathogenesis of IC/BPS. Methylhistamine and histamine are proposed biomarkers [4] [5] [6], while histamine receptor gene expression has been evaluated in IC/BPS patients [7]. Mast cell counts and physiology have also been investigated as part of this condition's pathophysiology [8] [9] [10] [11]. Monotherapies affecting histamine levels or receptor binding have been used to treat IC/BPS. Hydroxyzine (H1 receptor antagonist) has been used with some limited benefit [12] [13] and is often prescribed as a SOC treatment option. High dose cimetidine (H2 receptor antagonist) for one month was effective at symptomatic relief in a case series report of 9 patients [14]. Pentosan polysulfate is an active pharmaceutical ingredient (API) used in the treatment of IC/BPS, and it affects histamine release [2]. More re-

cently, its use has been limited given its potential for retinal side effects [15].

Histamine plays fundamental roles in modulating inflammation through increased capillary blood flow, vascular permeability, and cytokine release [16] [17]. Mast cells are the hosts for histamine, which can be released into the extracellular environment via mast cell degranulation [18] [19] [20]. Antihistamines are receptor antagonists or inverse agonists that act primarily downstream of mast cell degranulation. Histamine-1 (H1) receptor antagonists (e.g., cetirizine) are administered for allergies, whereas Histamine-2 (H2) receptor antagonists (e.g., famotidine) are administered to control acid in the stomach and heart burn. Prescription branded, generic, and over-the-counter (OTC) drugs of both classes of antihistamines are commercially available essentially worldwide. The OTC H1 and H2 antihistamines (cetirizine and famotidine, respectively) are deemed as exceptionally safe by the US Food and Drug Administration (FDA).

Treatments of diseases with drug combinations that include an H1 receptor antagonist and an H2 receptor antagonist have been successfully used in humans, such as urticaria [21] [22] [23] [24] and diarrhea [25] [26]. In 2020 we reported that a cohort of 110 severe and critical patients hospitalized with SARS-CoV2/Covid-19 were effectively treated with cetirizine plus famotidine, strongly suggesting a substantial reduction in symptom severity and mortality in high acuity Covid-19 patients [27]. It was proposed that the benefit of cetirizine 10 mg and famotidine 20 mg twice daily was due to reducing the pulmonary inflammatory "cytokine storm" downstream of histamine's action, which is common in patients with severe to critical symptoms [27] [28]. Consistent with our findings in humans, H1 + H2 dual antihistamine treatments were also successful using a porcine model of Pseudomonas-induced acute respiratory distress syndrome [29] and a guinea pig model of allergen-induced bronchial obstruction [30]. In aggregate there is a growing body of evidence of the effectiveness of H1 + H2 dual antihistamine therapies in treating diseases of histamine-mediated etiology, such as urticaria, diarrhea, and Covid-19.

In view of this body of evidence in other diseases we chose to test dual histamine receptor blockade as a treatment for IC/BPS, especially treatment-refractory cases, utilizing exceptionally safe APIs. Herein we provide preliminary evidence of the effectiveness of dual histamine receptor blockade in four female patients afflicted with IC/BPS and related symptoms.

2. Materials & Methods

A compounded pharmaceutical formulation was prepared according to US FDA 503A regulations. Number 1 gelatin capsules were prepared by extemporaneous compounding containing cetirizine HCl 8 mg and famotidine 22 mg, plus inert pharmaceutical excipients (e.g., lactose). The selected doses are similar, but not identical to, the US FDA approved daily doses for each API as OTC monotherapies (*i.e.*, cetirizine HCl at 10 mg and famotidine at 20 or 40 mg).

Four adult female patients aged 25 - 57 and afflicted long-term with IC/BPS

(and related urogynecologic conditions) were assessed in the office by a physician. Each patient was deemed as suitable for this compounded medication, based upon self-reported symptoms, medical history, diagnoses, and especially in view of prior SOC medical treatments (or procedures) that provided insufficient symptomatic relief. They were treated orally once daily with compounded cetirizine 8 mg - famotidine 22 mg. The patients were reassessed at subsequent office visits or by phone.

3. Results

Case 1: A 25-year-old female with a medical history of at least 8 years and diagnoses of IC/BPS, chronic irritable bowel syndrome-diarrhea (IBS-D), postural orthostatic tachycardia syndrome (POTS), and possibly Crohn's disease, had previously taken multiple NSAIDs, esomeprazole (proton pump inhibitor), and sucralfate (antacid) without resolution of her urologic and/or gastrointestinal conditions. The patient experienced painful, frequent urination 15 - 20 times per day with incontinence. She described her bladder pain and diarrhea symptoms as 9/10 in severity with significant lifestyle disruption. She was unable to sleep through the night and experienced total disruption of her job. Her work up revealed no significant abnormalities in physical exam or laboratory evaluation.

She was re-assessed by another physician for the uncontrolled IBS-D and was prescribed a compounded pharmaceutical formulation of cetirizine 8 mg plus famotidine 22 mg in an orally ingested gelatin capsule that was administered once daily.

Thereafter the patient experienced substantial reduction in her gastrointestinal symptoms, consistent with the dual antihistamine treatment benefits observed in other IBS-D patients [25] [26]. In addition, her IC/BPS symptoms were much improved, which prior to that date had not been achieved by NSAIDs or other medications. As further evidence of the beneficial effects, the patient requested and received multiple refills of the compounded H1 and H2 receptor antagonist combination medication. Her IC/BPS symptoms remained markedly improved, however they recurred whenever she stopped the compounded combination therapy. Using this treatment, her IC/BPS symptoms no longer interfered with her job or lifestyle, thus providing an improved quality of life.

Approximately three years later, by verbal interview, she described her improvement as "life changing" and reported "at most a 2/10" symptom severity for both IC/BPS and IBS-D. The patient's symptoms recurred if she discontinued treatment with the H1 and H2 receptor antagonist combination medication for 4 - 5 days. She continued to obtain refills of the compounded medication. She stated, "I tell all my (*location*) friends about my miracle medicine." This has been the only effective treatment and prophylaxis for her persistent IC/BPS symptoms. Furthermore, the H1 + H2 compounded medication was well tolerated, with no complications.

Case 2: A 47-year-old female with a diagnosis of at least 5 years duration of

IC/BPS manifesting as pain in the bladder, vagina, occasionally bilateral flanks, vestibulodynia, and cramping. Additionally, the patient experienced severe, painful urinary urgency resulting in frequent urination once per hour and once nightly nocturia. Work up for infection and intrinsic bladder pathology was negative. Prior to presentation, she was previously treated with phenazopyridine, the H1 antihistamine hydroxyzine, and/or acetaminophen.

She was prescribed a compounded pharmaceutical formulation of cetirizine 8 mg plus famotidine 22 mg in an orally ingested gelatin capsule that was administered once daily. In addition, she was started on calcium glycerophosphate (for regulation of dietary acid), while continuing to use hydroxyzine, an H1 antihistamine that is prescribed off-label for IC/BPS.

At follow up 6 weeks thereafter the patient reported that she had experienced substantial reduction in her bladder pain symptoms while taking the cetirizine-famotidine combination. As further evidence of the beneficial effects of the H1 + H2 receptor antagonist combination, the patient reported a reduction in urinary frequency to every 2.5 hours, no nocturia, and only mild urgency. She continued to administer the compounded cetirizine-famotidine drug combination thereafter, as it provided ample symptomatic relief, whereas prior treatments, such as the H1 antihistamine hydroxyzine alone, had been insufficient.

At follow up 6 months later she stated that she is doing very well and feels "normal". At that time, urinary frequency was every 2 hours with no nocturia, and normal urinary urgency. She was advised to continue the cetirizine-famotidine combination and hydroxyzine. Furthermore, the H1 + H2 compounded medication was well tolerated, with no complications.

Case 3: A 57-year-old female manifested symptoms of multi-year duration of bladder pain and overactive bladder, along with other physiologic and mental health disorders. At an office visit one year prior to starting the dual antihistamine combination, the patient expressed that she experienced severe and painful urinary urgency resulting in frequent urination once per 0.5 hour (30 minutes), nocturia 6 times per night, and without incontinence.

Multiple medications, such as Uribel® (a five-drug combination), gabapentin, calcium glycerophosphate, oxybutynin, phenazopyridine, oxycodone, pentosan polysulfate, dicyclomine, and the H1 antihistamine loratadine, and multiple procedures (bladder instillations, cystoscopy with hydrodistention, and intravesical onabotulinumtoxin A injections) were attempted to address her bladder disorder. However, polypharmacy and the multiple procedures failed to ameliorate the severity of this patient's chronic disease state.

Therefore, H1 + H2 histamine receptor blockade was attempted for this recalcitrant condition. She was prescribed a compounded pharmaceutical formulation of cetirizine 8 mg plus famotidine 22 mg in an orally ingested gelatin capsule that was administered once daily, in addition to hydroxyzine.

At follow up 3 months thereafter the patient reported that she had experienced reduction in her bladder pain while taking the cetirizine - famotidine

combination. As further evidence of the beneficial effects of the H1 + H2 receptor antagonist combination, the patient reported a reduction in urinary frequency to every 1.5 hours, nocturia 4 - 5 times nightly, and moderate urgency. At follow up 9 months after starting cetirizine - famotidine she stated that her bladder pain was minimal. Urinary frequency was every 2.5 hours, nocturia 3 times nightly, with mild-to-moderate urinary urgency. She was advised to continue the cetirizine-famotidine combination, hydroxyzine, and gabapentin.

Note that the symptomatic relief achieved by the compounded dual-histamine receptor blockade had not been achieved by prior daily treatments with loratidine, an inhibitor of the H1 receptor or pentosan polysufate that blocks the release of histamine. Thus, monotherapies directed at either histamine action or release had not been effective. Furthermore, the H1 + H2 compounded medication was well tolerated, with no complications.

Case 4: A 42-year-old female who manifested at least 5 years duration of chronic pelvic and bladder pain was assessed by a physician. She reported that the symptoms began after a series of presumptive urinary tract infections, although it was uncertain whether these were culture proven. She reported severe and painful urge to urinate, with frequent urination once per 0.5 hour (30 minutes), nocturia 2 times per night, and without incontinence. In an attempt to alleviate her pain symptoms, she had previously been prescribed gabapentin and hydrocodone/acetaminophen.

Upon presentation, she was prescribed a compounded pharmaceutical formulation of cetirizine 8 mg plus famotidine 22 mg in an orally ingested gelatin capsule that was administered once daily, in addition to hydroxyzine 25 mg once daily.

At follow up 3 months thereafter (by phone) she reported that her symptoms had "improved by 65 percent", and that she was currently only administering the cetirizine-famotidine combination for this urologic condition. Hydroxyzine was only administered as needed. She intended to continue to obtain refills of the compounded cetirizine-famotidine prescription. Furthermore, the H1 + H2 compounded medication was well tolerated, with no complications.

The aggregate results of the four cases are summarized in Table 1.

Table 1. Summary of four cases of IC/BPS in females. Urination frequency at baseline (pre-treated); urination frequency while treated daily with cetirizine 8 mg - famotidine 22 mg; bladder pain while treated daily with cetirizine 8 mg - famotidine 22 mg.

Case	Age	Frequency - Baseline	Frequency - Treated	Pain - Treated
1	25	1.0 hr	less frequent	reduced to 2/10
2	47	1.0 hr	2.5 hr	substantially reduced
3	57	0.5 hr	2.5 hr	substantially reduced
4	42	0.5 hr	less frequent	reduced by 65%

4. Discussion

In this proof-of-principle study, four adult female patients experiencing bladder pain and frequent and/or urgent urination were treated daily with an H1 receptor antagonist and an H2 receptor antagonist. Cetirizine (8 mg) plus famotidine (22 mg) in combination once daily was effective at reducing the level of pain, the frequency of urination, and other urogynecologic symptoms.

As summarized in Table 1, all four females diagnosed with severe IC/BPS for multiple years duration experienced baseline frequent (daytime) urination every 30 - 60 minutes. The frequency was reduced (improved) during cetirizine plus famotidine treatment in the four patients, with Cases 2 and 3 stating a substantial reduction to 2.5 hours. In addition, the four patients reported a substantial reduction in pain, with Case 1 stating the level of pain reduced from 9/10 to only 2/10, and with Case 4 stating the pain was reduced by 65%. However, given this was a physician-led retrospective review of the patients' files, a written pain questionnaire was not administered, but it would have been advantageous. The treatment benefits were demonstrated to endure for months (Cases 2, 3, and 4) to years (Case 1). The symptomatic treatment benefits waned after discontinuing the "maintenance" medication in Case 1, although this variable is unknown for the other three women. The cetirizine plus famotidine dual drug combination was superior in efficacy to prior use of monotherapies directed at the histamine pathways in Cases 2 and 3. In all four females the medication provided near-term effective treatment of acute urination frequency and pain symptoms, followed by maintenance of the improved conditions, thus, demonstrating both a treatment effect and a prophylactic effect. In all four cases the medication was well tolerated, with no complications.

The historic safety in humans around the globe for antihistamines, such as cetirizine and famotidine, provide a distinct advantage to this IC/BPS combination therapy. OTC approvals by the US FDA and other foreign regulatory agencies are merited for only the safest of medications in view of historic pharmaceutical surveillance. Millions of patients in the US alone routinely administer OTC H1 or H2 receptor antagonist medications effectively and safely. For instance, cetirizine is designated as an OTC dosage form at 10 mg and famotidine is an OTC at 10 or 20 mg. The selected doses are under the maximum daily doses for each API as US FDA-approved OTC medications, namely cetirizine at 10 mg maximum daily and famotidine at 40 mg maximum daily.

IC/BPS patients may respond to H1 + H2 dual antihistamine treatment within several days to several weeks. Treatment should be carried out for enough time to substantially resolve or reduce the symptoms (e.g., pain or frequent urination). Patients may administer the combination for the acute treatment and/or prophylaxis (maintenance) of IC/BPS symptoms. Although once daily cetirizine - famotidine combination is likely to be exceptionally safe and well tolerated, the anticipated possible minor side effect of cetirizine in some patients is mild sedation, which is common for H1 antihistamines. Therefore, administration at bed-

time is recommended.

Although not tested in this limited physician-sponsored study, we speculate that the dual drug treatment might beneficially affect the structure and health of bladder tissue by blocking the action(s) of histamine.

5. Conclusions

Based upon the proof-of-principle evidence from these 4 female IC/BPS patients, treatment once daily with the selected H1 + H2 receptor antagonist combination therapy: 1) can reduce the severity of bladder pain; 2) can reduce urination symptoms, such as frequency of urination, nocturia, and urinary urgency; 3) can serve as a prophylactic "maintenance" medication; 4) can reduce symptom severity in patients who have previously administered H1 antihistamine monotherapy with little or no success; 5) can improve quality of life parameters; and 6) can achieve symptomatic relief at doses that do not exceed the US FDA approved daily doses for OTC monotherapies, which are already deemed as exceptionally safe.

Limitations: 1) This is a proof-of-principle case series of only four female patients using retrospective reviews of patient files; 2) Randomized controlled trials are recommended to ascertain the level of efficacy regarding acute treatment vs. long duration prophylaxis (maintenance), female vs. male, with or without a concomitant SOC medication, as well as the level of disease acuity and/or comorbidities that might impact the beneficial effect that is strongly suggested by this case series; 3) It is recommended that future prospective studies include a standard questionnaire, such as the Pain Urgency Frequency or O'Leary-Sant instruments.

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Human Subjects

A physician sponsored study of a prescription medication (compounded or approved) in a limited number of patients may be conducted at the discretion of the physician(s) using his/her professional judgment concerning patient care and treatment options. Institutional Review Board approval is not required for individual case reports and case series with a limited number of patients. The four patients gave their consent to the public disclosure of their research results and the patients' identities are not disclosed.

Author Contributions

RBH: conceptualization, compounding pharmacy, clinical investigation, data curation, and manuscript review; PHM: clinical investigation, data curation, data

analysis, and manuscript revision; DP: conceptualization and manuscript review; TPD: conceptualization, data analysis, principal author, manuscript revision. All authors agreed to the publication of the manuscript.

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Conflicts of Interest

RBH discloses a patent application on dual-histamine receptor blockade in the treatment of IC/BPS, other patents and/or patent applications on dual-histamine receptor blockade in the treatment of diarrhea and Covid-19, and is a shareholder in Hista Rx LLC; PHM has no conflicts of interest to disclose; DP discloses a patent application on dual-histamine receptor blockade in the treatment of IC/PBS, and is a shareholder in Hista Rx LLC; and TPD discloses a patent application on dual-histamine receptor blockade in the treatment of IC/BPS, and is a shareholder in Hista Rx LLC. The patent application on dual-histamine receptor blockade in the treatment of IC/BPS is assigned to Hista Rx LLC.

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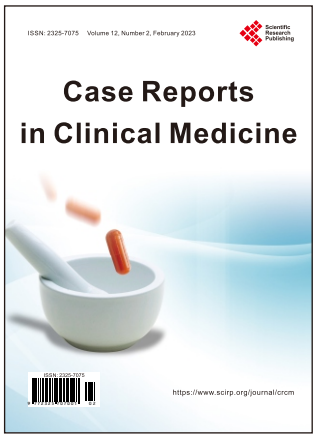
Abbreviations

H1 is histamine type-1; H2 is histamine type-2; IC/BPS is Interstitial cystitis/Bladder pain syndrome; OTC is over-the-counter; SOC is standard of care; NSAID is non-steroidal anti-inflammatory drug.



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