Case Reports

Intestinal Lymphangiectasia in a Patient with Autoimmune Polyglandular Syndrome Type III

Bipul Kumar Choudhury*, Uma Kaimal Saikia†, Dipti Sarma‡, Bikash Narayan Choudhury***, Sarojini Dutta Choudhury†, Dhiren Saharia*, Mihir Saikia*

Abstract

Autoimmune polyglandular syndromes (APS) comprise a wide clinical spectrum of autoimmune disorders. APS is divided into Type I, Type II, Type III and Type IV depending upon the pattern of disease combination. Chronic diarrhoea is one of the many manifestations of APS and many aetiological factors have been suggested for it. Apart from the established aetiological factors, intestinal lymphangiectasia may be responsible for chronic diarrhoea in some cases. Intestinal lymphangiectasia has been reported in Type I APS. We report a case of Type III APS with hypocalcaemia and hypothyroidism who had chronic diarrhoea of long duration and was finally diagnosed to have intestinal lymphangiectasia.

Introduction

The Autoimmune Polyglandular Syndrome (APS) encompass a wide clinical spectrum of disease with monogenic and complex genetic aetiologies.1 APS is characterized by the coexistence of at least two glandular autoimmune mediated diseases.2 Two major subtypes of APS, types I and II are defined according to age of presentation, characteristic patterns of disease combinations, and different modes of inheritance. APS I, also known as the autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia syndrome (APECED), is rare and usually manifests in infancy or childhood at age 3-5 or in early adolescence and, therefore, is also called juvenile autoimmune polyendocrinopathy.3 It is inherited as an autosomal-recessive condition and has a female to male ratio between 0.8:1 to 2.4:1.4 The clinical diagnosis of APS I classically requires the presence of two of the three cardinal components: chronic mucocutaneous candidiasis, autoimmune hypoparathyroidism, and autoimmune adrenal failure. Only one of these manifestations is required if a sibling has the syndrome. Patients of APS I are at risk for developing autoimmune diseases affecting almost every organ.5 Thus patients can present with hypoparathyroidism, Addison’s disease, gonadal failure, alopecia, vitiligo, type 1 diabetes, diarrhoea, intestinal malabsorption, pernicious anaemia, chronic active hepatitis and hypothyroidism. Perheentupa et al mentioned presence of intestinal malabsorption in 18% cases in a series of 89 Finnish patients.6 Amongst various causes of diarrhea and malabsorption in APS I, intestinal lymphangiectasia has also been mentioned as one. APS II is defined by the presence of primary adrenocortical insufficiency with either autoimmune thyroid disease (Schmidt’s syndrome) or type I diabetes (Carpenter syndrome) in the same individual. It is more common with a prevalence of 1 in 15,000 and has a female to male ratio of 1:3. Other manifestations like pERNICIOUS ANAEMIA, gonadal failure, vitiligo, alopecia, malabsorption including celiac disease also occurs with variable frequency. A third type called APS III has also been described and is characterized by association of autoimmune thyroid disease with an additional autoimmune disease other than Addison’s disease.7 Hasimoto’s thyroiditis is the commonest form of autoimmune thyroiditis seen in APS III. APS III is also associated with celiac disease, hypogonadism and myasthenia gravis. However to our knowledge there is no report of association of intestinal lymphangiectasia in Type III APS.

We report a case of Type III APS who presented with hypoparathyroidism, hypothyroidism and chronic diarrhoea who was subsequently diagnosed as a case of primary intestinal lymphangiectasia.

Case Report

A 35 year old female presented with history of paraesthesia of limbs and frequent episodes of carpopedal spasms for the last 10 years. She also complained of frequent loose motions for the same duration. Stools were of large volume, watery in consistency without blood or mucus. There was also a history of anasarca for the last 6 months. The symptoms started insidiously, six months after her first delivery. The paresthesia and carpopedal spasm was followed by an episode of generalized tonic clonic seizure. Investigations at that time revealed hypocalcaemia, primary hypothyroidism and low PTH levels. She was put on oral calcium, vitamin D, levothyroxine and phenobarbitone. But because of financial constraints her compliance to therapy was poor. Though she did not have any further seizure she continued to have frequent loose motions requiring occasional hospitalization where she was treated with antibiotics and intravenous fluids. All her symptoms dramatically subsided during her second pregnancy four years back, only to recur a few days postpartum. She also gave a history of secondary amenorrhoea for the last one year.

On admission she was found to be emaciated with anaemia, hypotension, anasarca and positive Trousseau’s sign. Her secondary sex characters were normal. Investigations revealed hypocalcaemia (4.9 mg/dl, corrected calcium level: 7.94 mg/dl) and severe hypoaIbuminaemia (0.2 gm/dl). Random blood sugar was 105 mg/dl. Total leucocyte count was 6050/cu.mm and differential leucocyte count (DLC) showed 14.9% lymphocytes. Repeat DLC after two days showed only 5% lymphocytes. Her serum TSH was 24.4 mIU/L (0.4-4.0), T4: 64 nmol/L (57.9-161), anti TPO antibody: 345 IU/dl (>100 positive) and PTH < 2.5 pg/ml (14-72). Serum FSH was 2.5 mIU/ml (2.8-11.3), LH 1.22 mIU/ml (1.1-11.6), prolactin 16 ng/ml (2.5-17), and morning 8 A.M. Cortisol 19.5 ngm/dl (5-25). IgA antibody for tissue transglutaminase was done and found to be negative. Ultrasonography of the abdomen showed moderate ascites and bilateral pleural effusion. An upper gastrointestinal endoscopy was done which showed scattered whitish patches in the duodenum suggestive of lymphangiectasia (Fig. 1). Biopsy from these lesions showed tissue lined by highly proliferative

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and malabsorption. Celiac disease has also been described in APS. With Candida or Giardia lamblia may also contribute to diarrhea. Intestinal infection has also been suggested as a cause of diarrhea. Intestinal infection of APS 1 and may account for steatorrhea in some patients. 10,11


departed for a meal, leading to failure of the physiologic stimulus for normal gall bladder contraction and pancreatic enzyme secretion and subsequent malabsorption. Endocrine cells of duodenal mucosa produce cholecystokinin and serotonin. Whereas cholecystokinin stimulates pancreatic enzyme secretion, serotonin increases gut motility. 9 Autoimmune destruction of serotonin secreting cells has also been suggested as a cause of diarrhea. Intestinal infection with Candida or Giardia lamblia may also contribute to diarrhea and malabsorption. Celiac disease has also been described in APS.

Intestinal lymphangiectasia have been reported in patients of APS 1 and may account for steatorrhea in some patients. 3,11

Discussion

Autoimmune polyglandular syndrome can present with various manifestations. Diarrhoea and malabsorption occurs in 18% cases. Our patient also had chronic diarrhoea and was malnourished with a BMI of 15.1 kg/m2 and albumin level of 0.2 gm/dl. Many causes of chronic diarrhea and malabsorption in APS has been suggested. In most cases, the diarrhea is secondary to hypoparathyroidism and results from hypocalcemia, as it does sometimes in hypoparathyroidism of other etiologies. 6 Diarrhea impairs absorption of calcium and the calciferol drugs, worsening the diarrhea and making the hypocalcemia difficult to control by oral medication. Hypocalcemia also impairs the secretion of cholecystokinin by the duodenal mucosa in response to a meal, leading to failure of the physiologic stimulus for normal gall bladder contraction and pancreatic enzyme secretion and subsequent malabsorption. Endocrine cells of duodenal mucosa produce cholecystokinin and serotonin. Whereas cholecystokinin stimulates pancreatic enzyme secretion, serotonin increases gut motility. 9 Autoimmune destruction of serotonin secreting cells has also been suggested as a cause of diarrhea. Intestinal infection with Candida or Giardia lamblia may also contribute to diarrhea and malabsorption. Celiac disease has also been described in APS.

Intestinal lymphangiectasia have been reported in patients of APS 1 and may account for steatorrhea in some patients. 3,11

Intestinal lymphangiectasia is a disorder characterized by diffuse or localized ectasia of the enteric lymphatics often in association with lymphatic abnormalities elsewhere in the body. It was originally described in 1961 by Waldmann et al. Ecatic lymphatics may be located in the mucosa, submucosa or subserosa, leading to loss of protein and lymphocytes into the gut or the peritoneal cavity. Intestinal lymphangiectasia is one of the causes of protein losing enteropathy and can present with loose motions, hypoproteinaemia, fat malabsorption, edema and lympho cytopenia. 13 Our patient had severe hypoproteinaemia, anasarca, lymphopenia and frequent loose motions. Loose motions persisted even after normalization of calcium levels. Intestinal lymphangiectasia may be primary as described by Waldmann et al or secondary to intestinal obstruction. A low-fat diet associated with medium-chain triglyceride supplementation is the cornerstone of primary intestinal lymphangiectasia medical management. Long-chain fatty acids lead to chylomicrons, obstructing lymphatics and increasing lymphatic pressure and lymphocyte loss. The absence of long-chain fatty acid in the diet prevents chyle engorgement of the intestinal lymphatic vessels thereby preventing their rupture with its ensuing lymph loss. Medium-chain triglycerides are more water soluble and absorbed directly into the portal venous circulation and avoid lacteal overloading. 14,15 Other inconsistently effective treatments have been proposed for intestinal lymphangiectasia patients, such as antiplasmin, octreotide or corticosteroids.

Our patient had hypothyroidism and hypoparathyroidism without evidence of adrenal insufficiency and hence she is a case of APS III; although we could not estimate anti-adrenal antibodies. To the best of our knowledge intestinal lymphangiectasia has not been reported in association with APS III earlier. This case suggests that intestinal lymphangiectasia may be a component of APS III also and should be kept in mind as one of the differential diagnoses of chronic diarrhoea in APS.

References

Acute Pancreatitis in a Case of Falciparum Malaria-A Rare Presentation

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Abstract

Various complications including multiorgan failure is not uncommon in Falciparum malaria. But acute pancreatitis is a very rare complication in falciparum malaria. We describe here such a patient who suffered from acute pancreatitis and multiorgan failure.

Introduction

Plasmodium falciparum infection is known to be associated with a spectrum of systemic complications ranging from mild and self-limiting to life-threatening. But pancreatitis in a case of malaria is a very rare complication and only few case has been reported so far. We described here such a patient with malaria complicated with pancreatitis.

Case Presentation

A 35 years male patient resident of Basirhat, West-Bengal admitted with history of high grade fever associated with chills and rigor for last 5 days. Patient experienced pain around epigastrium with radiation towards back from the very beginning of fever. From day 2 he was passing high color urine associated with yellow discoloration of eyes and nausea. His urine volume started decreasing from day 4 of onset of symptoms. He was non alcoholic, non smoker, non diabetic and non hypertensive. No past history of jaundice, gallbladder disease.

On examination patient was conscious oriented, had moderate degree of pallor and icterus. His pulse rate was 100/min regular, B.P-150/60, respiratory rate was-22/min. on systemic examination patient had epigastric and right hypochondrial tenderness, and just palpable liver and spleen. Other findings were within normal limit. His investigations report summarized in Table 1. Of note were decreasing levels of Hb and increasing levels of urea and creatinine starting from day of admission. Marked hyperbilirubinemia (17.5) with normal SGOT (49), SGPT (40), ALP (419) with very high levels of Amylase (783) and Lipase(2255). HBsAg, anti-Hcv, anti-HAV, anti-HEV all were negative. His serum lipid profile was normal. Peripheral blood smear was positive for plasmodium falciparum with marked parasitaemia of 40%. In USG report there were bulky pancreas, biliary tract normal and CT abdomen report suggested acute pancreatitis (Fig. 1).

Course in the Hospital

The patient was put on parenteral Artesunate immediately on admission along with broad spectrum antibiotics. Proper fluid, nutrition and electrolyte balance were maintained.

His urine output drastically reduced and developed disorientation. He was sent for Hemodialysis and shifted to ICCU but his condition was deteriorating progressively and expired.

Discussion

Abdominal pain often reported in falciparum infections. Mehta SR et al in their study conducted on 425 cases of falciparum malaria 3.29% presented with pain abdomen.3

The causes of abdominal pain in malaria are protein and include acalculus cholecystitis,2 splenic rupture,4 splenic infarction,4 splenic torsion,5 Hepatitis /hepatemegaly Khalid Mahmood et al in their analysis of 348 malarial cases observed pain abdomen in 23(21.29%) and 9(8.33) with acute abdomen simulating the picture of acute pancreatitis but serum amylase and ultrasound exclude the diagnosis of acute pancreatitis.6

Though abdominal pain is frequent in falciparum malaria , in this case pain abdomen was due to acute pancreatitis which
In this case pain abdomen is due to acute pancreatitis, which is an unusual cause of abdominal pain in malaria with very few case reported worldwide. Multi organ failure in severe falciparum malaria as was in this case in not a rare complication. But pancreatitis as part of multi organ failure is very rare. Several hypothetical mechanisms has been described for the pathogenesis of pancreatitis including capillary blockage by parasitized RBC and acute hemolysis. Only two case reports of patient suffering from acute pancreatitis as complication of falciparum malaria are available so far from India. In one case Seshadri P et al described a 21 year old male patient suffered from acute pancreatitis and bilateral subdural haematomas. Another case reported by PSA Sharma, R Shasi Kumar in which a 17 year old male patient from central India suffered from acute pancreatitis.

**Conclusion**

Though pain abdomen is not uncommon in Falciparum malaria but pain abdomen due to pancreatitis is a very rare life threatening complication. This should be kept in mind in making a differential diagnosis of pain abdomen in a patient suffering from falciparum malaria as it carries a very poor prognosis.

**Acknowledgement**

We are thankful to Prof. Amit Kumar Banerjee, H.O.D Dept. of Medicine, Medical College Kolkata for giving permission for publication of this case report. We also indebted to the patient’s relatives for their co-operation to prepare this report.

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Unilateral and Painless Development of Isoniazid Induced Gynecomastia during Re-treatment of Pulmonary Tuberculosis


Abstract
A case of isoniazid induced gynecomastia is being reported in an 18-year old male, who received a re-treatment regimen for the relapse of pulmonary tuberculosis (TB). At the end of two months of the treatment, the patient developed a painless unilateral gynecomastia, which completely disappeared after a month of the cessation of isoniazid. A review of literature on isoniazid induced gynecomastia is discussed.

Introduction
Gynecomastia is an enlargement of the male breast due to benign ductal and stromal proliferation. It can occur physiologically in three phases of life which are the neonatal period, puberty and old age. The maternal estrogens are responsible for its occurrence in the first phase, while the reduction of endogenous testosterone synthesis has been associated with the development in the latter two phases. Gynecomastia can also be caused pathologically in a number of diseases, as well as, by drugs. While 10-20% of cases are drug-induced, 25% are reported to be idiopathic. We describe below a rare case of an isoniazid induced unilateral painless gynecomastia, which developed during the course of re-treatment TB.

Case Report
An 18-year old unmarried male, who had taken 6 months of anti-TB treatment (ATT) in the past without the occurrence of side effects, was found to be suffering from sputum smear positive pulmonary TB and was put on Category II ATT with a daily administration of 0.75g of streptomycin (S), 300mg of isoniazid (H), 450mg of rifampicin (R), 1.5g of pyrazinamide (Z) and 800 mg of ethambutol (E). No other medical illness co-existed. At the end of 2-month intensive phase, sputum smear conversion took place, following which streptomycin was stopped. However, the patient developed a painless right sided gynecomastia (Fig. 1) without any associated complaint. The swelling was 8 cm X 6 cm sized, soft in consistency, non-tender and freely mobile. Left breast was normal and systemic examination revealed no abnormality. Routine haematological investigations like haemogram, total leucocyte count, differential leucocyte count, platelet count and absolute eosinophil count, and biochemical profile consisting of random blood sugar, liver and kidney function tests and serum electrolytes were within normal limits. Evaluation of secondary sexual characters and external genitalia was found to be normal. Serum levels of testosterone, estrogens, follicle stimulating hormone (FSH), leutinising hormone (LH) and cortisol were advised following the endocrinologist’s consultation. However, serum estrogen level could not be measured owing to unavoidable reasons. The serum hormonal levels were found to be normal except serum testosterone which was observed to be low as shown in Table 1.

Isoniazid was suspected to be the culprit drug and withdrawn from the treatment regimen, while other drugs were continued. After a month of its cessation, the swelling disappeared completely (Fig. 2). The patient was put on the continuation phase consisting of rifampicin and ethambutol without isoniazid for the total period of one year throughout which the patient remained asymptomatic.

Discussion
Case reports of isoniazid-induced gynecomastia have by far been few. The first case of painless gynecomastia was reported in 1953 by Guinet P et al from France following the introduction of isoniazid. Thereafter, sporadic TB cases have been shown to develop gynecomastia during the course of treatment with isoniazid. Recently, development of isoniazid induced / associated bilateral gynecomastia has been reported from India in a case of tubercular pleural effusion on Category I ATT and in a sputum positive pulmonary TB case on Category II ATT. Both cases had a painful gynecomastia that resolved either completely or partially on discontinuation of isoniazid. On the other hand, our case had a unilateral painless gynecomastia that developed on an isoniazid containing Category II ATT administered for the treatment of smear positive pulmonary TB and resolved completely after the discontinuation of isoniazid.

An endocrine imbalance is commonly considered to result in gynecomastia. This is so because estrogens stimulate breast tissue and androgens antagonize the effect. Therefore, an increase in estrogen or a reduction in testosterone would alter the normal estrogen to androgen ratio. Apart from the three physiologic phases of life, gynecomastia can be caused pathologically in a large number of diseases having deficient production or action of testosterone (congenital anorchia, Klinefelter syndrome, androgen resistance, defects in testosterone synthesis, and conditions resulting in a secondary testicular failure), increased estrogen production (testicular tumors, carcinoma lung, true hermaphroditism) and an increase in peripheral aromatase or its substrate (adrenal disease, liver disease, starvation and thyrotoxicosis). The disorder can also be caused by drugs, and at times, an idiopathic finding may be taken as normal.

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Drugs causing gynecomastia include estrogens (diethylstilbestrol, oral contraceptives, digoxin), gonadotrophins, inhibitors of testosterone synthesis and/or action (ketoconazole, alkylating agents, spironolactone, cimetidine). They mimic action of estrogens or testosterone to result in an endocrine imbalance. Other drugs like busulphan, ethionamide, isoniazid etc. can result in gynecomastia through unknown mechanisms. Theories have been postulated by various researchers into the mechanism of isoniazid induced gynecomastia. Slow acetylation was observed in a French report, in which, the authors hypothesized that a disturbance in vitamin B6 metabolism in liver could have caused the alteration in the estrogen–androgen metabolism. A “re-feeding” mechanism has been described in debilitated patients in whom restoration of weight causes normalization of hormonal function. The majority of reports have only described a temporal association of the drug with gynecomastia through unknown mechanisms. Theories have been postulated by various researchers into the mechanism of isoniazid induced gynecomastia. Slow acetylation was observed in a French report, in which, the authors hypothesized that a disturbance in vitamin B6 metabolism in liver could have caused the alteration in the estrogen–androgen metabolism. A “re-feeding” mechanism has been described in debilitated patients in whom restoration of weight causes normalization of hormonal function. The majority of reports have only described a temporal association of the drug with gynecomastia through unknown mechanisms.

### Table 1: Serum hormonal profile

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Measured Value</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>108.0 ng/dl</td>
<td>175-781 ng/dl</td>
</tr>
<tr>
<td>FSH</td>
<td>8.74 mIU/ml</td>
<td>1-10 mIU/ml</td>
</tr>
<tr>
<td>LH</td>
<td>7.9 mIU/ml</td>
<td>1-10 mIU/ml</td>
</tr>
<tr>
<td>Cortisol (8 A.M.)</td>
<td>16.40 mcg/dl</td>
<td>5-20 mcg/dl</td>
</tr>
</tbody>
</table>

Another notable feature of the case was the unilateral occurrence of gynecomastia. Majority of the case reports of isoniazid induced gynecomastia have found it to occur bilaterally. One of the possibilities could be that gynecomastia could begin unilaterally and become bilateral on the continuation of isoniazid, although it did not happen in our case since we had discontinued the drug. Another possibility could be that gynecomastia could commence bilaterally with an asymmetric enlargement of the breasts in such a manner that the disorder could be appreciated clinically only as a unilateral development and its bilateral existence could be confirmed only upon the conduct of a mammogram as noted in the Brazilian case report that observed a mildly painful enlargement of the right breast on an isoniazid containing ATT during re-treatment of TB but did not find any alteration in the left breast on a clinical examination.
Hypokalemic Periodic Paralysis due to Proximal Renal Tubular Acidosis in a Case with Membranoproliferative Glomerulonephritis

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Abstract

Proximal renal tubular acidosis (pRTA) is a rare disorder. Hypokalemia may be associated with it; occasionally leading to features like hypokalemic periodic paralysis. Though pRTA is a tubulointerstitial kidney disease, membranoproliferative glomerulonephritis may occasionally lead to pRTA by tubular damage through leaking proteins, cytokines or by inflammatory infiltrates. In our reported case a 27 year old male had recurrent episodes of hypokalemic quadriparesis. Investigations revealed features of pRTA including hypokalemia and non-anion-gap metabolic acidosis. His urine pH dropped to 5 with nH4Cl loading test. Kidney biopsy showed membranoproliferative glomerulonephritis with tubulointerstitial damage. Hypokalemic periodic paralysis and pRTA are uncommon associations of membranoproliferative glomerulonephritis.

Introduction

Proximal renal tubular acidosis (pRTA) is a rare disorder. Though it is associated with tubulointerstitial disease of kidney, primary glomerular diseases may also lead to pRTA from tubular damage by leaking proteins, cytokines or by inflammatory infiltrate. Hypokalemia is seen in distal RTA (dRTA) and less commonly in pRTA. Hypokalemic periodic paralysis (HPP) due to pRTA has not been described previously with membranoproliferative glomerulonephritis (MPGN).

Case Report

A 27 year old male Muslim patient presented with sudden onset flaccid paralysis of all four limbs for last two days without any sensory loss and bowel or bladder involvement.

He was normal four months back. Then he developed bilateral swelling even three weeks after the cessation of therapy in one of the Indian reports has been the development of a left sided swelling even three weeks after the cessation of therapy in a case of isoniazid associated bilateral gynecomastia. We did not observe any bilateral occurrence of the disorder either during the administration of isoniazid or following its cessation over the subsequent course of therapy at least clinically. The exact reasons for these observations resulting in either a unilateral or the bilateral occurrence of isoniazid induced gynecomastia cannot be explained as the very mechanisms of its development remain unknown.

The present case highlights a need for the health providers to keep in mind the possibility of the occurrence of gynecomastia during the course of treatment with isoniazid containing ATT. A serum hormonal profile comprising of both androgen and oestrogen should be performed whenever possible or wherever the facilities exist. A mammogram is not routinely warranted in such cases and the discontinuation of isoniazid often suffices to make gynecomastia disappear.

References


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His initial blood report showed Hb 12.0 gm %, TLC 10800/ cu mm (neutrophil 78%, lymphocyte 18%, monocyte 3%, basophil 0%, and eosinophil 1%), blood sugar (fasting) 96 mg %, urea 66 mg%, creatinine 2.2 mg %, Na+ 138 meq/L, K+ 2.08 meq/L. ECG showed T wave flattening. Urine examination revealed albumin +++, pus cells 2-4/hpf, blood +, and sugar +. His 24 hour urinary protein excretion was 6.149 gm. USG abdomen showed bilateral enlarged kidneys and increased cortical echogenicity.

Assuming a case of hypokalemic paralysis, potassium supplementation was given and the patient improved in his muscle power within two days. Anti-hypertensives (amlodipine and enalapril) and syrup potassium chloride were continued.

Repeat investigations showed Hb% 9.9 gm %, blood sugar (fasting) 86 mg%, urea 59 mg %, creatinine 2.78 mg %, Na+ 138 meq/L and K+ 2.78 meq/L. Urine examination showed PH 6.0, sp gravity 1015, albumin +++, Sugar ++, pus cells 2-4/hpf, blood +, and sugar +. His 24 hour urinary protein excretion was 4.1 gm. Serum cholesterol was 354 mg%. Serum albumin was 2.9 gm %. His arterial blood gas (ABG) analysis showed pH 7.27, PO2 96 mm Hg, PCO2 31 mm Hg, HCO3 15.4 meq/L, Na+ 139 meq/L, K+ 2.8 meq/L, Cl 117.6 meq/L (normal 102-109 meq/L) and anion gap = 6 meq/L (normal 6-12 meq/L). A non-anion-gap hyperchloremic acidosis with hypokalemia in this case suggested the possibility of RTA. We did ammonium chloride loading test by giving ammonium chloride 100 mg/kg orally. ABG analysis and urinary pH estimation were done hourly for six hours. His ABG analysis showed gradual increase in acidosis as pH 7.28 at 0 hour (baseline), 7.23 at 2 hour, 7.22 at 4 hour, and 7.22 at 6 hour; while urinary pH measured by pH-meter showed 6.5 at 0 hour (baseline) 5.5 at 2 hour, 5 at 4 hour, and 5.5 at 6 hour. The result was suggestive of pRTA. Persistent glycosura in spite of normal blood sugar value also pointed to proximal tubular reabsorption abnormality.

HbsAg, Anti HCV and HIV were non reactive. ANA and anti dsDNA were negative. ANCA was non-reactive. C3 was low. The kidney biopsy with immunofluorescence study showed MPGN (also known as mesangiocapillary glomerulonephritis) with predominant Ig G and C3 deposition. IgM deposition was also seen. There was interstitial oedema, mixed inflammatory cells infiltrate and focal tubular degeneration. Many of the tubules showed vacuolar degeneration. Tubules contained hyaline and granular casts (Figures 1 and 2 showed kidney biopsy with hematoxylin and eosin staining). Finally the patient was diagnosed to have tubulointerstitial disease as a consequence of MPGN that leads to pRTA with subsequent hypokalaemia and recurrent flaccid paralysis.

**Discussion**

Proximal RTA (pRTA or, type II RTA) is caused by failure of proximal tubular cells to reabsorb filtered bicarbonate from urine. This results in urinary loss of HCO3- causing systemic acidosis with inappropriately high urine pH. As the distal intercalated cells function normally, acidosis is less severe than dRTA. In pRTA urine may become acidified to a pH of less than 5.5 (especially in presence of low plasma bicarbonate) in contrary to dRTA. Bicarbonate is replaced in the circulation by chloride (Cl-). Increased distal Na+ delivery results in hyperaldosteronism with consequent renal K+ wasting and hypokalemia. Urine analysis may reveal abnormal levels of phosphate, calcium, glucose, and amino acids.

Proximal RTA has several causes including familial disorders like cystinosis, galactosemia, glycogen storage disease (type I), hereditary fructose intolerance, Lowe syndrome, tyrosinemia, and Wilson’s disease. Other causes include multiple myeloma, amyloidosis, medullary cystic disease, Sjogren syndrome, primary hyperparathyroidism, vitamin D deficiency, paroxysmal nocturnal hemoglobinuria, toxins such as lead and cadmium, drugs such as ifosfamide, outdated tetracycline, aminoglycosides, acetazolamide and tenofovir-based antiretroviral therapy. Fanconi’s syndrome is a generalised dysfunction of proximal tubular cells where there is also phosphaturia, glycosuria, aminoaciduria, uricosuria and tubular proteinuria. Principal feature of Fanconi’s syndrome is bone demineralization (osteomalacia or rickets) due to phosphate wasting.

Though RTA is a tubulointerstitial kidney disease, it may also be seen in primary glomerulopathies. Distal RTA has been described in membranous nephropathy and SLE nephritis with proteinuria.\(^1,2\) Nephrotic syndrome has been described as a cause of pRTA.\(^3\) Our case also had pRTA resulting from MPGN with nephritic range proteinuria.

Primary glomerulopathies may cause damage to tubules and interstitium with functional derangement. Potential mechanisms of tubulointerstitial injury include glomerular leak of plasma proteins toxic to epithelial cells, glomerulus-derived cytokines activating the tubule epithelial cells, reduced peritubular blood flow leading to tubulointerstitial ischemia and hyperfunction of remnant tubules.\(^4\) Occasionally, the same inflammatory mechanism of glomerulonephritis may affect the tubules also.\(^4\) For example, in SLE nephropathy, deposits of immune complexes may be seen in tubular basement membranes. Similarly, in anti-glomerular basement membrane disease (anti-GBM disease) antibodies are reactive against tubular basement membranes also. Osteopontin, a cell attachment glycoprotein may have
An Interesting Case of Cardiotoxicity due to Bufotoxin (Toad Toxin)

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Abstract

Consumption of toads for their aphrodisiac effect is a common practice in Laos, China and in some parts of India. Toad secretions from parotid and skin contains toxin similar to cardiac glycosides. It results in bradycardia and cardiac dysfunction leading on to death in some cases. We report a case of toad poisoning in a young previously healthy male.

Introduction

Toads are amphibians that are used in Chinese medicines for their aphrodisiac effect.1 The toad secretions contain a toxin named as bufotoxin which has cardiac glycoside like activity.2 The toxicity manifests as gastrointestinal and cardiac disturbances. Bufotoxin acts by inhibiting sodium – potassium ATPase pump3 resulting in cardiac dysfunction, hypotension, electrolyte abnormality, arrhythmias and may result in death. We report a case of bufotoxicty due to consumption of toads presenting with abdominal pain, hypotension and Bradycardia.

Case Report

A 26 year old male was admitted for acute abdominal pain and vomiting in the surgical unit. While undergoing evaluation for acute abdomen he developed hypotension and bradycardia, was transferred to Intensive Care Unit. The patient was hypotensive with a BP of 70/50 mm Hg, pulse rate was 50/min. Examination of other systems were normal except for priapism. He was put on ionotropic support and atropine. Patient developed pulmonary edema on the same night and was intubated for ventilatory support.

His hematological report revealed leucocytosis, 24500 cells/ cu.mm with neutrophils 82.2%, lymphocytes 6.9%, monocytes 6.8%, eosinophils 2.7 % and basophils 1.4%. Serum amylase was 47 U/l (22- 80 U/l) and lipase 17 U/l(< 60 U/l). Blood urea nitrogen was 29 mg/dL and serum creatinine was 1.7 mg/dL. Serum sodium was 133 meq/L and potassium level was elevated by 15.4 meq/L. Investigations suggested prTA.

Conclusion

Primary glomerulopathies, like MPGN may cause tubulointerstitial damage with subsequent development of prTA. Periodic paralysis with hypokalaemia is common in dRTA but it may also be seen in prRTA. HPP due to prRTA is a rare association of MPGN.

References

to 5.7 mmol/L. ECG revealed bradycardia with a heart rate of 54/mt. Cardiac enzymes troponin I was positive CK MB was 83 IU/L. Chest Xray showed cardiomegaly with bilateral midzone infiltrations suggestive of pulmonary edema and echocardiogram showed LV dysfunction with ejection fraction of 48% with mild global hypokinesia. Patient was empirically treated as a case of myocarditis.

The patient was managed symptomatically and could be successfully weaned off from ventilator. Echocardiogram repeated on the fourth day showed normal LV function with an ejection fraction of 60%. Recounting the events which lead to the illness, the patient revealed consumption of 5-6 toads on the eventful morning for aphrodisiac effect. The patient was discharged on the seventh day of admission.

Discussion

The toads contain several toxic substances that includes cardioactive agents, catecholamines, indolealkylamines and non-cardiac sterols. Bufotoxin is a cardio active agent with digitalis like effect and it also bears a structural similarity to digitalis. The toxins are located in the skin and parotid glands of the toad and they are transferred to the human by ingestion of a toad as a whole or in parts. The toxin can produce varied manifestations, commonly gastrointestinal like nausea, vomiting and abdominal pain. Digitalis like effect results in bradycardia, conduction block, ventricular tachycardia and sudden death. Seizures have been reported. The exact mechanism of priapism is not known. The proposed mechanism is ingestion of canthardin, a toxin found in Spanish flies (beetles). Historically, this canthardin accumulate in toads after consuming these beetles. Consumption of toads hence result in priapism. This is the most probable mechanism.

Prominent laboratory features are hyperkalemia and increased digoxin concentration which is attributable to the cross reactivity of toad venoms with digoxin in serum immunoassays. Serum levels of potassium leave a prognostic significance in determining the mortality. In severe cases, digoxin specific Fab antibodies have been found to be useful. Calcium gluconate which is regularly used in the management of severe hyperkalemia should not be used in toad toxicity since it aggravates the toxicity. In our patient the hyperkalemia was transient and mild not necessitating any specific management.

A Case of Primary Ciliary Dyskinesia with Pulmonary Arterial Hypertension Responding to Oral Sildenafil

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Abstract

Primary ciliary dyskinesia (PCD) is an autosomal recessive heterogeneous group of conditions with variable clinical findings like recurrent respiratory tract infections, bronchiectasis, situs inversus, singly or in various combinations. Development of Pulmonary arterial hypertension can be a late complication of this disease. Here we present a case of PCD with recurrent respiratory tract infections, bronchiectasis and severe PAH, who responded to treatment with Oxygen, IV broad spectrum antibiotics and oral sildenafil.

Introduction

Primary ciliary dyskinesia (PCD) is an autosomal recessive disease with extensive genetic heterogeneity characterized by abnormal ciliary motion and impaired mucociliary clearance. Ultrastructural and functional defects of cilia result in the lack of effective ciliary motility, causing abnormal mucociliary clearance. This leads to recurrent or persistent respiratory infections, sinusitis, otitis media, and male infertility. In 46% of the patients, it is associated with situs inversus.

In 1933, Kartagener described a unique syndrome characterized by the triad of situs inversus, chronic sinusitis, and bronchiectasis, which was dubbed Kartagener syndrome. Later, patients with this condition were noted to have defects in the ultrastructure of cilia. Afzelius coined the term immotile cilia. Later studies showed that disorganized motion, rather than immotile cilia, resulted in the uncoordinated and ineffective ciliary beat, hence the term ciliary dyskinesia syndrome (CDS). These patients often develop pulmonary arterial hypertension. Aggressive treatment of pulmonary arterial hypertension, at least in initial stages, shows good response and reversibility.

Treating hypoxic pulmonary vasoconstriction with vasodilators aggravates the ventilation/perfusion mismatch (decrease in arterial oxygenation). There are also associated side effects of systemic hypotension. The inhalative route of application is superior because of the pulmonary enrichment of the applied agent (pulmonary selectivity). Furthermore, a preferential deposition in the well-ventilated areas of the lung.
Case Report

HS, 26 year, male from Howrah district of West Bengal was admitted with insidious onset of limb swelling leading to anasarca in 3 months. There was associated decrease in urination. He also had shortness of breath and was NYHA class IV symptomatic on admission. He gave a history of recurrent cough and cold since 4-5 years of age. The episodes were 10-15 times in a year, more in winter months and required medical attention but not requiring hospitalization. Cough was accompanied by productive sputum. There was no history of hemoptysis.

He is a non-smoker, still unmarried. There is no history of drug abuse particularly of anorexients. He also denied history of allergy to any particular substance. He did not maintain any pets.

On admission, he was orthopneic, cyanosed with congested eyes (Figure 1). Clubbing was grade II (Figure 2). He had a barrel shaped chest wall. Clinically, he had features of pulmonary hypertension with right heart failure. PASP was in the tune of 90 mmHg on echo. There was associated systemic hypotension which required inotropic support. Biochemically, he had type II respiratory failure with spO2 of 65%, Hb of 16 gm% and TLC 16,500/cumm. We kept him on Oxygen, iv diuretics, iv broad spectrum antibiotics, low dose digitalis and Sildenafil 25mg bd. With treatment, his spO2 increased to 80% with oxygen, systemic pressure improved and he went off inotropes, edema decreased and he had NYHA functional improvement to class III.

To elucidate the cause of pulmonary hypertension, we ruled out any left to right shunt and possible Eisenmenger by doing contrast echo and later TEE. We also checked the autoantibodies (ANF, P-ANCA, C-ANCA, RF) to rule out any connective tissue disorders. We performed a CT thorax which revealed panacinar emphysema with bilateral focal bronchiectatic changes involving the lower and middle lobes (Figure 3). α1 anti-trypsin was in the normal range. He had a positive saccharin test.

We next performed a ciliary motility study by looking at the sperm motility. All the sperms were found to be non-motile. Thus with normal visceral situs, bronchiectatic changes and absent ciliary motility, we could establish a diagnosis of primary ciliary dyskinesia in this patient.

Discussion

Primary ciliary dyskinesia (PCD) is an autosomal recessive heterogeneous group of conditions with variable clinical findings. The disease phenotype is caused by defects of respiratory cilia, sperm tails, and cilia of embryonic node.

Currently 3 genes (DNA II, DNAH5 and DNAH11) that encode for dynein proteins (axonemal and cytoplasmic) have been linked to recessive primary ciliary dyskinesia. It is hypothesized that given the small number of well characterized affected families, the large size of the dynein genes, the different dynein proteins present in the axoneme, and the large number of regulatory structural proteins necessary for ciliary function, dynein mutations may not be the only cause of primary ciliary dyskinesia. Since its initial description in 1933, Kartagener’s syndrome (triad of situs inversus, bronchiectasis, and either nasal polyps or recurrent sinusitis) and the description of Afzelius in 1975 of the defects in the dynein arms underline this condition, incomplete forms of the syndrome have increasingly been recognized. Thus, clinical findings may be varied in patients with Primary ciliary dyskinesia, including respiratory distress in neonates, recurrent respiratory tract infections, bronchiectasis, situs inversus, heterotaxia, infertility, and hydrocephalus, singly or in various combinations. The study by Noone et al. looking at 94 patients from 68 families, showed that cough was present in 100% of patients, bronchiectasis (98%), sinusitis (47%), otitis media (92%) and situs inversus (46%).

Exhaled NO may be used as a screening test, with levels of NO being characteristically low. Ciliated epithelial cells obtained from the inferior or middle turbinate using a sterile cytology brush may be studied for ciliary beat pattern and frequency using digital high speed video imaging, when the dyskinetic cilia are seen to lack the classical sideway recovery sweep. Axonemal structure of respiratory cilia may be visualized by transmission electron microscopy and defects in dynein arms, peripheral and central tubules, radial spokes, and basal bodies may be seen.

Development of pulmonary arterial hypertension can be a late complication of this disease, if patient survives to adulthood. Treating hypoxic pulmonary vasoconstriction with vasodilators aggravates the ventilation/perfusion mismatch as well systemic hypertension. The inhaled route of application is superior because of the pulmonary enrichment of the applied agent (pulmonary
selectivity). Furthermore, a preferential deposition in the well-ventilated areas of the lung is achieved (intrapulmonary selectivity). However, inhaled pulmonary vasodilators like Nitric oxide or Iloprost are either costly or locally unavailable in every setup. There are case reports of oral sildenafil causing preferential pulmonary vasodilation and improving gas exchange in patients with severe lung fibrosis and secondary pulmonary hypertension.

Pulmonary vascular resistance index is reduced by nitric oxide (-21.9%, 95% CI -14.1 to -36.2), epoprostenol (-36.9%, -24.4 to -59.6), and sildenafil (-32.5%, -10.2 to -54.1). However, ratio of pulmonary to systemic vascular resistance is decreased only in individuals who received nitric oxide and sildenafil. Prostacyclin increased V/Q mismatch (shunt 16.8%, 10.8-35.9; low V/Q 3.8%, 0.0-13.0) and decreased arterial oxygenation. By contrast, nitric oxide and sildenafil maintained V/Q matching, with raised arterial partial pressure of oxygen (14.3 mm Hg, -1.7 to 31.3) noted for sildenafil. So sildenafil causes preferential pulmonary vasodilation and improves gas exchange in patients with secondary pulmonary hypertension due to lung pathology. We, in this case could also demonstrate good response to oral sildenafil.

Primary ciliary dyskinesia is in itself a rare clinical entity. Demonstrating pulmonary arterial hypertension and showing favorable response with oral sildenafil is indeed a rare and precious opportunity which we wish to share with our fellow colleagues.

References
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Deep Vein Thrombosis and Euvolemic Hyponatremia in a Hypothyroid Patient

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Abstract
Hypothyroidism is a procoagulant state; hypothyroid females have greater risk of DVT than hypothyroid males. We present a case of primary hypothyroidism who presented with euvolemic hyponatremia and DVT that required thyroxine replacement and correction of hyponatremia. This highlights that hypothyroidism can present as euvolemic hyponatremia and deep vein thrombosis.

Introduction
Hypothyroidism predisposes to both euvolemic hyponatremia and hypercoagulability, former due to decreased cardiac
output and diminished free water restriction and the latter through increase in factor VIIa levels. We hereby report a case of primary hypothyroidism presenting with hyponatremia and venous thrombosis.

Case Report

48yr old female admitted with complaints of right side thigh/gluteal pain in orthopedics ward in our hospital. X - ray hip was normal. She was treated with NSAIDS. She gave history of tiredness, cold intolerance, increased sleep, poor memory, constipation, weight gain for which medical opinion was obtained. She was not a diabetic or hypertensive. Her examination revealed a dull face, non-pitting pedal edema, dry skin, Pulse rate of 64/min, blood pressure measuring 130/70 mm/Hg, her blood routine, renal functions tests were normal. Serum (Sr) Total T3: 17.36ng/dl (80-180ng/dl), Sr. Total T4: 1.02µg/dl (4.5-12.5µg/dl), Free T3: 0.35pg/ml (1.4-4.4), Free T4: 0.17ng/dl (0.7-2.0 ng/dl), TSH: 91.65mIU/ml (0.3-5.0mIU/ml), suggestive of primary hypothyroidism. She was started on thyroxine 100 µg/day. One week later, again our opinion was obtained for the low Sr. sodium. Her Sr. Sodium -118meq/l. On further evaluation her Sr. Osmolality is 238.8, urine osmolality - 520, urine sodium 22 meq/l. indicating euvolemic hyponatremia. She was not having any clinical features suggestive of hyponatremia except a generalized apathy. Her thyroxine dose was increased to 150µg/day. Her Sr. Sodium gradually improved to 132 meq/l over a period of four days without administering hypertonic saline.

Meanwhile her low back ache with thigh pain became severe. Her lower limb Doppler study showed right femoral vein thrombosis (Fig. 1). Following was her coagulation profile results. Homocysteine - 4.5 µmol/lit, (normal 0 to 12 µmol/l), antithrombin III-50 µg /ml (normal), protein C - 82 units /ml (normal 67-195u/ml), protein S - 75 u/ml (normal 55-123 u/ml). Factor V eiden mutation was not detected. Her platelet count, prothrombin time and activated partial thromboplastin time were within normal limits and ANA screening was negative. There was no family history of coagulative disorders.

She was started on low molecular weight heparin and later substituted with warfarin. Meanwhile thyroxine replacement was continued. Patient became asymptomatic and her pain got reduced. Further investigations could not be done, as the patient was lost to our follow-up.

Discussion

This lady presented with euvolemic hyponatremia due to hypothyroidism. The mechanism by which hypothyroidism induces hyponatremia is incompletely understood. The principal abnormality in the patient with normal fluid intake appears to be the inability to maximally suppress antidiuretic hormone. This is most likely due to reduced cardiac output in this disorder, which can lead to the release of antidiuretic hormone via the carotid sinus baroreceptors. The glomerular filtration is also decreased in hypothyroidism. This can directly diminish free water excretion by diminishing water delivery to the diluting segments. Decreased delivery may be particularly important in those cases in which hyponatremia develop despite appropriate suppression of ADH release. Regardless of the mechanism, the net effect of the impairment in water excretion is the retention of ingested water and a reduction in the plasma sodium concentration by dilution. It should be treated with thyroid supplements only and there is no need to replace with hypertonic saline. Patients with sub clinical hypothyroidism had significantly higher level of Factor VII: C. The greater increase in Factor VII: C compared to that of Factor VII: Ag as shown by the increase in their ratio, might reflect the presence of activated Factor VIIa. This might mean a hypercoagulable state which could contribute to the increased prevalence of venous thrombosis. A hypercoagulable state might be another argument in favour of thyroxine replacement treatment in subclinical hypothyroidism especially in patients with additional risk factors for vascular disease. Antithrombotic prophylaxis in patients with severe hypothyroidism, however, should be viewed with caution because of a possible hyperfibrinolytic state in such patients. In our case this could not be done as the patient was lost to our follow-up.

Conclusion

This case highlights that hypothyroidism should be considered as one of the causes of euvolomic hyponatremia and deep vein thrombosis especially in women where other causes for these conditions could not be traced.

References