Primary amyloidosis of the larynx

Anurag Daudia, M Motamed, S Lo

Abstract
Primary laryngeal amyloidosis is a rare benign disease of unknown aetiology. It can present with dysphonia or stridor. A woman presenting with airway compromise, who required a tracheostomy, is reported.


Keywords: laryngeal disease; amyloidosis

Case report
A 47 year old woman presented with a seven year history of dysphonia which had deteriorated recently. Fibre optic laryngoscopy showed polyps on the right false vocal cord with a suggestion of subglottic stenosis (fig 1). The true vocal cords were mobile and appeared normal.

While awaiting further investigation, she presented with airway compromise requiring urgent tracheostomy. Direct laryngoscopy revealed subglottic oedema. The polypoid lesion was biopsied and showed features suggestive of amyloidosis and this was confirmed after staining with Congo red. A flexible bronchoscopy through the tracheostomy tube showed isolated nodules within the trachea (fig 2). Full blood count and erythrocyte sedimentation rates were normal.

At follow up a year later she was noted to have a change in voice. Fibre optic laryngoscopy showed new lesions on the right and left true vocal cords. These were resected with a carbon dioxide laser. The result was a subjective improvement in the quality of her voice and airway. She was decannulated two months later. She remains under review and requires no further intervention.

Discussion
Amyloidosis is a benign, slowly progressive condition that is characterised by extracellular fibrilar proteins. Diagnosis is confirmed by histopathological specimens that stain with Congo red. Amyloidosis can be classified as either primary, developing spontaneously, or secondary to some other longstanding inflammatory disease such as rheumatoid arthritis. The primary form can be further subdivided into a localised form, where deposits are confined to a single organ or location, or generalised, where deposits are found to some extent in all tissues.

The most common presenting symptoms of primary laryngeal amyloidosis are dysphonia and stridor. Rarely, airway compromise occurs and an alternative airway may be necessary. The presence of tender bones, lymphadenopathy, or splenomegaly should alert the clinician to the possibility of generalised amyloidosis. Microscopic examination reveals pinkish grey masses lying under the intact epithelium, either as nodular masses or subepithelial deposits.

Learning points
- Amyloidosis is a rare benign disease of unknown aetiology.
- Laryngeal amyloidosis can present with hoarseness or stridor which may require tracheostomy.
- Histological diagnosis from a biopsy specimen can be confirmed with characteristic staining with Congo red.
- Treatment is by surgical resection using the carbon dioxide laser. Repeated resections may be necessary.
Localisation of lesions in the larynx is to the ventricle, false vocal cords, true vocal cords, aryepiglottic folds, and subglottis in that order of frequency. Histology of the biopsied specimen using routine haematoxylin and eosin stain shows amyloid as eosinophilic extracellular infiltrate. Further staining with Congo red reveals characteristic apple green birefringence with a polarising microscope confirming the diagnosis.

Treatment of localised laryngeal amyloid deposits is by surgical removal. Several authors have reported good results using the carbon dioxide laser. This disease is slowly progressive and repeated removal may be required. The carbon dioxide laser has been shown to be more effective than conventional surgery because it minimises trauma. Regular follow up is important as its recurrent nature may require repeated resections using the carbon dioxide laser.

Extensive psoriasis induced by interferon alfa treatment for chronic hepatitis C

C Taylor, D A Burns, M J Wiselka

Abstract

A 47 year old man with chronic hepatitis C was treated with interferon alfa, 3 million units three times a week, and developed widespread plaque psoriasis within weeks of starting interferon therapy. There was no previous history of psoriasis. The psoriasis was characterised by extensive nail involvement and plaques at the interferon injection sites. The patient relapsed after a total of 12 months of interferon and was subsequently treated with interferon and ribavirin (ribavirin) with recurrence of the psoriasis.

(Keywords: hepatitis C; interferon alfa; psoriasis)

Case report

A 47 year old white man was found to have hepatitis C infection after presenting with abnormal liver function tests. There was a history of intravenous drug use 15 years previously. Serum was positive for hepatitis C virus RNA, genotype 1a using the polymerase chain reaction (PCR), and a liver biopsy specimen showed severe inflammatory changes with probable cirrhosis (Knodell score = 11). There was no past history of skin disease or family history of psoriasis.

He was treated with interferon alfa-2a (Schering-Plough) at a dose of 3 million units (MU) three times a week, and received a total of 12 months of treatment. His transaminase levels reverted to normal and serum hepatitis C virus RNA was not detected while on treatment.

Interferon was initially well tolerated, but three months after starting treatment he presented with severe psoriasis affecting the entire body and scalp. Nail changes were particularly striking and there were plaques of psoriasis over his injection sites (figs 1 and 2).

Figure 1 Severe nail dystrophy associated with psoriasis induced by interferon.
The patient was very keen to continue interferon, despite the psoriasis, in view of his apparent good response to treatment. His psoriasis was treated with emollient, a topical preparation containing betamethasone valerate and coal tar, calcipotriol, and psoralen/ultraviolet irradiation (PUVA) therapy with some benefit; but it remained extensive while he was receiving interferon. He had no evidence of any autoimmune disease while on treatment, although cryoglobulins IgG and κ were detected in the serum.

The psoriasis settled completely after stopping interferon, but the hepatitis C relapsed with the PCR test becoming positive six months after cessation of treatment. He subsequently received a combination of interferon alfa-2a, 3 MU three times a week, and tribavirin (ribavirin) 1200 mg daily with widespread recurrence of the psoriasis, again requiring topical preparations and PUVA treatment.

Discussion

Interferon is now licensed for the treatment of several conditions including chronic hepatitis C. Moderate cutaneous reactions during treatment with interferon alfa are relatively common and include itching, urticaria, dryness, and hair loss.4

In 1986, Quesada and Gutterman reported three cases of psoriasis aggravated by interferon alfa which was used in the treatment of disseminated malignant disease.5 A further three cases were reported by Hartmann et al in 19896 and the first report of psoriasis associated with interferon alfa-2a and a further three reports of psoriasis associated with other alfa interferons.

In the cases reported in the literature exacerbations of psoriasis usually occurred between one and six weeks after initiation of treatment with interferon but could occur as long as six months after starting interferon treatment. In the majority of cases the psoriasis continued to deteriorate while on interferon leading to discontinuation of treatment. Withdrawal of interferon leads to an improvement in psoriasis and the close temporal relationship between the onset of psoriasis and interferon alfa treatment suggests that the drug may act as a triggering agent. The mechanisms by which interferon may cause a flare up of psoriasis are unclear but could involve an interaction between interferon and other cytokines.

The unusual features in this patient included the lack of any previous history or family history of psoriasis, the extensive nail involvement, and the active plaques around the injection sites. We were able to continue interferon treatment despite the extensive psoriasis, which was treated with topical agents and PUVA therapy. It is of note that the psoriasis was worse over the interferon injection sites, which raises the interesting question of whether this was the result of high local concentrations of interferon or Koebner’s phenomenon, when the skin disease appears in response to traumatic injury.

This case demonstrates that psoriasis may be induced or aggravated by interferon treatment for chronic hepatitis C and patients who are known to have psoriasis should be warned about this before starting treatment. Psoriasis rapidly improves when interferon is discontinued, but it is possible to continue interferon during a flare-up of psoriasis if the skin is treated actively.

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Histoplasmosis of the small bowel in patients with AIDS

Milton A Gumbs, Hanasoge Girishkumar, Arshad Yousuf, Leo Levy, Mayank Patel, Vijay Narasimha

Abstract

Two cases of jejunal strictures caused by Histoplasma capsulatum in AIDS patients are presented. Both patients were intravenous drug abusers. One patient, who was being treated for Pneumocystis carinii pneumonia, presented with jejunal perforation and the other with lower gastrointestinal bleeding and intestinal obstruction. On exploration, both patients were found to have jejunal strictures; one had intestinal perforation, and the other had intestinal obstruction with ulcers and strictures resulting in gastrointestinal bleeding. In areas where it is endemic, histoplasmosis is rarely disseminated. Dissemination is most commonly seen in immunosuppressed patients. Dissemination and extrapulmonary histoplasmosis is now included in the case definition of AIDS.

Keywords: histoplasmosis; AIDS; jejunal perforation

Histoplasmosis is a fungal infection caused by Histoplasma capsulatum that is more commonly seen in endemic areas. Various gastrointestinal manifestations such as perforation, obstruction, and haemorrhage have been reported. With the increasing incidence of AIDS, more cases of histoplasma infection are being reported from non-endemic areas. Thus, it is now important to consider histoplasmosis in the differential diagnosis of immunocompromised patients with acute abdomen. Histoplasmosis is now included in the Centers for Disease Control case definition of AIDS.

Case reports

CASE 1

A 37 year old Hispanic man, with no recent history of visiting an area where histoplasmosis is endemic, presented with periumbilical abdominal pain of four months’ duration. The pain had worsened during the last two days and was associated with fever. He was a known intravenous drug abuser, had had AIDS diagnosed, and was being treated for Pneumocystis carinii pneumonia. On examination, the patient was febrile with tachycardia. His abdomen was distended, tender, rigid, and had no bowel sounds. Radiographs revealed gas under both domes of the diaphragm and distended loops of jejunum. The results of the blood count and biochemical analysis were within normal limits. On exploration, purulent fluid was found in the peritoneal cavity. There was stricture in the mid-jejunum; proximal to the stricture were distended loops of jejunum with perforation (fig 1). Mesenteric lymph nodes were enlarged. The diseased and perforated segment was resected and a primary anastomosis performed. The resected specimen showed focal accumulation of macrophages stuffed with yeast. The yeast form with a thin cell wall, but without a true capsule, was seen with methenamine silver stain. Postoperatively, the patient was treated with intravenous amphotericin B and made an uneventful recovery.

CASE 2

A 24 year old Hispanic man, a known intravenous drug abuser, was admitted with a history of fever of unknown origin. On examination he was found to have fever, right lower quadrant pain, and oral candidiasis, and blood results showed a lymphopenia and leucopenia. On exploration, distended loops of jejunum were found with a stricture in the distal jejunum obstructing the lumen. There was mesenteric adenopathy. The strictured segment was resected and a primary anastomosis performed. Histology of the lymph nodes showed the cells were overloaded with characteristic yeast form. The tissue showed localisation of activated mononuclear phagocytes with numerous yeast...
forms (fig 2). Gross examination of the resected specimen revealed deep linear ulcers at the site of the stricture, which was responsible for massive bleeding. Postoperatively, the patient was treated with intravenous amphotericin B. Transbronchial biopsy revealed *H capsulatum*. The patient later developed disseminated histoplasmosis, which proved fatal.

**Discussion**

In 1908, Darling first described the diseased caused by *H capsulatum*, a dimorphic fungus. The second case report, by Crumrine and Kessel, was published in 1931. Nearly 30 years after the original report, in 1934, De Monbream described the cultural characteristics of the fungus. Since then, many reports have described various facets of the disease.

Histoplasmosis, an endemic disease in the United States, is prevalent in the Ohio-Mississippi Valley. Infection of the human host is by the inhalation of spores. After inhalation, 99% of people who are exposed develop a self limiting lesion that is similar to the Ghon complex seen in tuberculosis. Occurrence and resolution of the lesion passes as an asymptomatic incident. Once exposed, people become sensitised to the fungus and the skin test becomes positive. In a few, the disease can become disseminated. These individuals usually have some associated risk factors such as old age, lymphoma, immunosuppression, or chronic disease. There is a 25% association of disseminated histoplasmosis with underlying immunodeficiency disorder. However, it is interesting to note that disseminated histoplasmosis is increasing in patients with AIDS in areas where histoplasmosis is not endemic.

Gastrointestinal involvement of histoplasmosis is seen at necropsy in 75% of patients with disseminated disease. Clinically, 20% of patients with dissemination are asymptomatic. Pulmonary lesions usually precede the gastrointestinal involvement. However, an alternate route of infestation, unlike swallowing spores, has been suggested in patients with isolated gastrointestinal involvement. Often in disseminated histoplasmosis the entire gastrointestinal tract is involved, although segmented involvement also is reported. Intestinal lesions include pseudopolyps and ulceration either constricting or perforating diffuse granulomatous lesions.

Ulceration of the gastrointestinal tract occurs anywhere from the nasopharynx to the rectum. In a review of the literature beginning in 1906 we found 10 reported cases of histoplasma infection presenting as stricture of a segment of the stomach, ileum, or colon. The distal ileum is the most common site involved, followed by colon and stomach. Ours are the first reported cases of jejunal stricture in patients with AIDS. There is one case report from Africa of a case caused by *H duboisa* (African histoplasmosis) in a 36 year old Nigerian women. However, this patient did not have any immunosuppressive factors. Heneghan et al reported a case of ileal stricture with perforation in a patient with AIDS.

Colonic granuloma presenting as an abdominal mass mimicking carcinoma of the colon is reported by Haggerty et al. Gastrointestinal presentation of histoplasmosis has no specific symptomatology. It can present with bloody diarrhoea, which can cause confusion with ulcerative colitis, or Crohn’s disease, as in our case, and can cause intestinal obstruction, perforation, or gastrointestinal bleeding. In fact, we considered tuberculosis of the intestine as the differential diagnosis of our patient with stricture and lymphadenopathy.

The diagnosis of the gastrointestinal histoplasmosis usually requires tissue for culture or histological identification of the infecting organism. Detection of the antibodies to *H capsulatum* has shown not to be accurate in patients with AIDS. Wheat et al have described the use of radioimmunoassay histoplasma polysaccharide antigen for the diagnosis of disseminated histoplasmosis. A positive histoplasma skin test in areas where histoplasmosis is endemic, however, is not of much use because the population generally has been sensitised, but it may be of importance in other areas. In patients with AIDS, however, the test has not been reliable. Untreated histoplasmosis has a mortality rate of 83%. The optimal treatment of disseminated histoplasmosis in the AIDS population has not been firmly established. Intravenous amphotericin has been effective over a prolonged period of time. Some investigators have found oral antifungal agents to be effective in immunocompromised patients with disseminated histoplasmosis, and others have found less success and relapse rates as high as 25% in patients with AIDS. The current recommended treatment includes intravenous amphotericin during the rapidly progressive phase of the disease followed by maintenance therapy with amphotericin B given weekly oritraconazole twice a day.

In summary, gastrointestinal histoplasmosis is not a commonly considered diagnosis in AIDS patients presenting with gastrointestinal symptoms. The fact that the infection has increasingly been reported in AIDS patients in areas where histoplasmosis is not endemic makes it important that this diagnosis be
Pseudovitamin D deficiency rickets—considered when dealing with an acute abdomen in AIDS patients.


Pseudovitamin D deficiency rickets—a report from the Indian subcontinent

Abdul Hamid Zargar, Ambish Mithal, Arshad Iqbal Wani, Bashir Ahmad Laway, Shariq Rashid Masoodi, Mir Ifthikhar Bashir, Mohammad Ashraf Ganie

Abstract

Pseudovitamin D deficiency rickets (also called vitamin D dependent rickets type I) is one of the types of inherited rickets and is caused by a deficit in renal 25-hydroxyvitamin D 1α-hydroxylase. This form of rickets has not been reported from the Indian subcontinent. Three patients with this disorder are presented. These patients were all females aged 3–20 years and presented with growth failure and skeletal deformities. All had florid clinical and radiological rickets. The biochemical abnormalities seen included hypocalcaemia, hypophosphataemia, and hyperphosphatasaemia. All patients had grossly raised 25-hydroxyvitamin D concentrations and markedly low to undetectable concentrations of 1,25-dihydroxyvitamin D. A disturbing feature of this study was the late referral of the patients.

(Keywords: 1α-hydroxylase; calcitriol; inherited rickets; vitamin D dependent rickets)

It is well recognised that it is the casual exposure to sunlight that provides most humans with their vitamin D requirement. A subset of patients with rickets and osteomalacia

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whose clinical and metabolic abnormalities are resistant to conventional therapeutic doses of vitamin D have been identified. This subset of patients is referred to as having vitamin D resistant rickets or, if pharmacological doses of vitamin D were therapeutically effective, vitamin D dependent rickets.

Pseudovitamin D deficiency rickets (or type I vitamin D dependent rickets) is an autosomal recessive disorder that may be due to impaired activity of 25-hydroxyvitamin D 1α-hydroxylase, the enzyme responsible for conversion of 25-hydroxyvitamin D (25(OH)D) to 1,25-dihydroxyvitamin D (1,25(OH)2D).1 In this report we present the data of three patients with pseudovitamin D deficiency rickets. To our knowledge no such data have been published from the Indian subcontinent.

Case reports
Three patients aged 3–20 years presented to the endocrinology department at the Sheri-Kashmir Institute of Medical Sciences, Srinagar, Kashmir (India) for growth failure, and variable features of rickets and bony deformities.

PATIENT A
A 3 year old girl, product of a consanguineous marriage, was brought to the endocrine clinic with the complaints of failure to thrive and delayed motor milestones. Clinical examination revealed a 71 cm tall, well nourished girl with mild frontal bossing, rachitic rosary, widening of wrists, and knock knees. Examination of respiratory, cardiovascular, gastrointestinal, and neurological systems was normal.

PATIENT B
A 7 year old girl, second in birth order, product of a normal vaginal delivery, was brought to medical attention with the complaint of

Table 1  Anthropometric parameters of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Chronological age (years)</th>
<th>Height (cm)</th>
<th>Expected height (cm)</th>
<th>Height age (years)</th>
<th>*Height SDS</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>3</td>
<td>71</td>
<td>93</td>
<td>1.0</td>
<td>−7.33</td>
</tr>
<tr>
<td>B</td>
<td>7</td>
<td>105</td>
<td>119</td>
<td>5.0</td>
<td>−3.58</td>
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<tr>
<td>C</td>
<td>20</td>
<td>124</td>
<td>159</td>
<td>8.0</td>
<td>−7.61</td>
</tr>
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</table>

*Height SDS = height standard deviation score.
Biochemical investigations

<table>
<thead>
<tr>
<th>Patient</th>
<th>Serum calcium* (mmol/l)</th>
<th>Serum phosphorus* (mmol/l)</th>
<th>Serum alkaline phosphatase* (IU/l)</th>
<th>Serum 25-hydroxyvitamin D (ng/ml)</th>
<th>Serum 1,25-dihydroxyvitamin D (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2.05</td>
<td>0.87</td>
<td>648</td>
<td>&gt;100</td>
<td>&lt;5</td>
</tr>
<tr>
<td>B</td>
<td>2.00</td>
<td>0.84</td>
<td>611</td>
<td>&gt;100</td>
<td>&lt;5</td>
</tr>
<tr>
<td>C</td>
<td>2.05</td>
<td>0.94</td>
<td>202</td>
<td>70</td>
<td>5.8</td>
</tr>
<tr>
<td>Normal range</td>
<td>2.25–2.63</td>
<td>0.97–1.45</td>
<td>30–120</td>
<td>8–80</td>
<td>16–65</td>
</tr>
</tbody>
</table>

*Mean of three estimations.
†Corrected for serum albumin.

Progressive deformity of lower limbs for two years. Clinical examination revealed widening of wrists and ankles with knock knees. Her systemic examination did not reveal any abnormality. She was 105 cm tall.

**PATIENT C**

A 20-year-old regularly menstruating woman was referred by an orthopaedic surgeon with unusual deformities of both legs and arms. She had sustained a fracture of her left tibia at 3 months of age and fractures twice thereafter, the last one at the age of 12 years. Thereafter, the patient had complained of progressive deformities of both lower limbs. Clinical examination revealed a young woman with normal secondary sexual characteristics. She had anterior bowing of tibia on both sides and deformities in the arms around the elbow joints.

The anthropometric data of the three patients are given in table 1. Full blood count, urinalysis, kidney and liver function tests, serum sodium and potassium, and ammonium chloride test (performed as recommended by Wrong and Davies) were normal in all the subjects. Detailed radiological screening of these patients revealed marked changes of rickets in long bones of arms and legs in patient A (fig 1); widened, frayed, and deeply cupped epiphyses of radius and ulna in patient B (fig 2); and marked smooth bowing of the long bones in legs and arms in patient C (figs 3 and 4). As shown in table 2, all patients had hypocalcaemia, hypophosphataemia, and hyperphosphatasia. Serum concentrations of 25(OH)D and 1,25(OH)2D, measured by specific radioimmunoassay, were normal to raised and low to undetectable respectively.

**Discussion**

Pseudovitamin D deficiency rickets is an inborn error of vitamin D metabolism. Vitamin D, synthesised in the skin and obtained from dietary sources, is 25-hydroxylated in the liver to 25(OH)D. In the proximal renal tubules, 25(OH)D is converted to 1,25(OH)2D, the biologically active metabolite of vitamin D. Pseudovitamin D deficiency rickets, also known as vitamin D dependent rickets type I, is an autosomal recessive disorder that may be due to impaired activity of 25-hydroxyvitamin D 1α-hydroxylase, a renal cytochrome P-450 enzyme of the vitamin D pathway.¹ Patients discussed in this report had developed rickets and other bony abnormalities in the absence of symptoms, signs, or laboratory evidence of malabsorption, hepatic or renal disease. Distal renal tubular acidosis constitutes an important cause of short stature and rickets in the Kashmir valley.³ However, a normal ammonium chloride test excludes that disorder. These patients had low serum calcium, low phosphorus, and low to undetectable 1,25(OH)2D in presence of normal to raised 25(OH)D. This suggests the diagnosis of pseudovitamin D deficiency rickets in all these patients.

Features of pseudovitamin D deficiency include hypocalcaemia, hypophosphataemia, short stature, skeletal deformities of rickets, dental enamel hypoplasia, and frequently marked increases of serum alkaline phosphatase activity; circulating concentrations of 1,25(OH)2D are low or undetectable.⁴ Before the availability of 1α-hydroxylated vitamin D metabolites, this disorder was treated with vitamin D or 25(OH)D. The doses of vitamin D (40–54.5 mg/kg/day) and 25(OH)D (3–18 mg/kg/day) required to achieve normocalcaemia and healing of rachitic lesions were approximately 100 times than those used for the treatment of dietary vitamin D deficiency.⁵ This disorder is inherited as an autosomal recessive trait. Two other types of inherited rickets include hypocalcaemic vitamin D resistant rickets (also known as type I vitamin D dependent rickets) in which the gene for vitamin D receptor is mutated⁶ and X linked hypophosphataemic vitamin D resistant rickets in which the PEX gene (phosphate regulating gene with homology to endopeptidase on the X chromosome) is mutated.⁷ Until recently the molecular basis of pseudovitamin D deficiency rickets had remained unclear, even though the disease locus has been mapped to chromosome 12q14 by linkage analysis.¹¹ However, in a recent study inactivating mutations in the 25-hydroxyvitamin D 1α-hydroxylase gene as a cause of pseudovitamin D deficiency rickets have been identified.¹² With the availability of 1,25(OH)2D (calcitriol), the treatment of this disorder has become simple; however, early diagnosis of this disorder is imperative to prevent major bony deformities as seen in our older patients.

**Learning points**

- Pseudovitamin D deficiency rickets, an uncommon form of rickets, has not been reported from India before.
- Biochemical findings include hypocalcaemia, hypophosphataemia, hyperphosphatasia, and low to undetectable concentrations of 1,25(OH)2D in the presence of normal to raised 25(OH)D concentrations.
- Treatment with calcitriol corrects biochemical abnormalities, induces healing of rickets, and restores the rate of skeletal growth.

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