Abstract

Chromosomal breakage syndromes are a group of genetic disorders that are ascribable to the autosomal recessive mode of inheritance. Xeroderma pigmentosum is one of the chromosomal breakage syndromes which is due to the involvement of deformity in the deoxyribonucleic acid’s nucleotide excision repair. Xeroderma pigmentosum is a genetic disorder, which is autosomal recessive, heterogeneous, and more common in cases of consanguinity, caused by mutations in at least 10 genes and 9 complementation groups. The disorder is very rare. Patients experience photophobia and extreme photosensitivity and have pigmetary changes in ultraviolet light-exposed areas of the body with freckling, premalignant, and malignant skin lesions arising in keratinocytes soon after the fleeting exposure to sunlight. Patients are also oversensitive to environmental mutagens such as cigarette smoke and possibly to the widely used agricultural insecticide, diazinon. Progressive neurological abnormalities along with some rare complications are also noticed among these patients. Symptoms and thoracic high-resolution computed tomography are considered for diagnosis. Only corticosteroids can be given to limit the progression of the disease. Xeroderma pigmentosum-related interstitial lung disease is one of the rarest forms and we thereby report an interesting case.

KEYWORDS: Xeroderma pigmentosum, interstitial lung diseases, corticosteroids

INTRODUCTION

The interstitial lung disease (ILD) describes a heterogeneous group of chronic disorders comprising of lung parenchyma and alveolar interstitium. Interstitial lung disease in pediatric patients is a varied group of rare respiratory disorders that are usually present in childhood and associated with significant morbidity and mortality. However, the presentation can sometimes be a delayed one and the manifestations may be evident in adolescence or early adulthood. This can be attributed to the slow progression leading to delay in seeking medical care. The pathogenesis of the distinct childhood ILD (ChILD) is complicated and implicates genetic contributors. Childhood interstitial lung disease incidence is arduous to assess, probably because the diagnosis remains cryptic in abounding situations without identifiable causes. This is embellished by prevalence estimates that extend from 0.1 to 16.2 cases per 100 000. Sometimes the etiology of ILD can be identified to be caused by inorganic and organic exposures, drugs, connective tissue disease, or smoking-related. However, the identification of such a cause is seldom seen in child. The clinical course of the child case is unforeseeable, with a decline in pulmonary functions punctuated by episodes of acute exacerbation. Various multisystem genetic disorders may have child as one of their components. Xeroderma pigmentosum (XP) is a rare genetic multisystem disorder affecting skin and lungs and also predisposes the patient to develop distinct malignancies. The elementary pathology in patients with XP is a breakdown of an enzyme involved in nucleotide excision repair (NER). Defective deoxyribonucleic acid (DNA) repair occurs after exposure to ultraviolet light (UV) light, customarily in the range of 290-320 nm or chemical carcinogens. Xeroderma pigmentosum-associated ILD is very rare and can present as microcephaly, cerebellar ataxia, growth retardation, skeletal abnormalities, hypogonadism, pancytopenia, abnormal pigmentation, and immunodeficiency’s.

CASE PRESENTATION

A 20-year-old male non-addict, the eighth child of non-consanguineous parents was referred from the medical ward in view of breathlessness to our outpatient department. He had a past history of pulmonary tuberculosis (TB) (presented with hemoptysis) at the age of 4 months old and was managed with anti-tubercular treatment for 1 year. He was symptomatic since childhood with complaints of dry cough, dyspnoea on exertion for 4 months (Modified Medical Research Council-MMRC grade 4), intermittent fever, and history of infective exacerbation 0-1/year, multiple skin pigmentation, and hypersensitivity to sunlight, and thus, he was diagnosed with XP. There was no history of chest pain. He had increased symptoms for 4 months with a complaint of dry cough, increased tremor, history of increased frequency of bowel movements, and intermittent fever. His general examination was within normal limits. Physical examination revealed bilateral crackles, and a 6-minute walk distance could not be performed. On investigation, his hemoglobin level was 13.3 g/dL and his total leucocyte count was 28 000 cells per cubic millimeter of blood, with neutrophils 80% and lymphocytes...
10%. Other biochemical parameters were within normal limits. Chest radiograph showed bilateral reticulonodular opacities (Figure 1). Serum immunoglobulin-E was 394. Human immunodeficiency virus, hepatitis C virus, hepatitis B virus, and serological tests were non-reactive. High-resolution computed tomography showed intra- and interlobular septal thickening, ill-defined ground glass opacities throughout lung parenchyma, widespread ill-defined centrilobular nodules, and scattered and patchy lobular air trapping (Figure 2). These features were consistent with ILD. As the patient was symptomatic since childhood, relapse TB and lung cancer were excluded as diagnosed clinically and radiologically due to the chronic duration of illness. Two-dimensional echocardiography revealed pulmonary artery systolic pressure of 40 mmHg. Spirometry showed a restrictive pattern with forced vital capacity (FVC) of 9% and Indian predicted (IP) of 10%. The patient was referred for expert neurology opinion to the in-house neuromedicine department, and the likelihood of neurological involvement was excluded by history and clinical examination. Ophthalmology reference was done to rule out squamous cell carcinoma of the eye and he was diagnosed as having early pterygium with prominent blood vessels. We excluded immunodeficiency-related lung infection (Pneumocystis pneumonia (PCP) and many others) by doing sputum examination for gram smear and culture, fungal smear, and culture and sputum for PCP. Bronchoscopy was planned but was not possible due to the deterioration in the patient’s clinical condition. Hematological malignancies were excluded by complete blood count and differential count and by taking expert hematological opinion. However, in view of patient being relatively symptomatic and lung function is very poor, trans-bronchial lung biopsy (TBLB) was not done. The genetic test was not performed due to financial restrictions. The final diagnosis was made as XP-associated ILD which was based on a multidisciplinary approach. Patient was started on tablets prednisolone 30 mg per day for 6 months followed by tapering for total duration of 6 months and fluconazole 200 mg stat followed by 100 mg per day for 10 days in view of XP with oral candidiasis. Patient was a candidate for long-term oxygen therapy and offered the same with other rehabilitation. Within few months after discharge, the patient died shortly at age of 20 years.

**DISCUSSION**

Xeroderma pigmentosum is an extremely rare autosomal recessive disorder (chromosomal breakage syndrome). It was first described by Moriz Kaposi in 1876. Xeroderma Pigmentosa is divided into eight subtypes with seven caused by a defect in the NER pathway (XPA, XPB, XPC, XPD, XPE, XPF, XPG) while the eighth (XPV) caused by a defect in DNA polymerase. It starts in early childhood and severe changes occur as pigmentary changes in UV-exposed areas of the body and cutaneous photosensitivity. Incipient exposure may result in skin cancer development. The skin ages prematurely frequently over sun-exposed area, look dry, and contain both hypo and hyperpigmented regions. Our patient was also having multiple skin pigmentation and hypersensitivity to sunlight since childhood. There is a defect in the DNA repair mechanism. In children younger than 3 years, severe changes appear and become progressively more severe. Patients experience photophobia and extreme photosensitivity and have pigmentary changes in UV-exposed areas of the body with freckling, premalignant, and malignant skin lesions. Patients are also hypersensitive to environmental mutagens such as cigarette
smoke and possibly to the widely used agricultural insecticide, diazinon. Patients due to UV radiation exposure are prone to develop central nervous system (CNS) tumors, which manifest as a neurodegenerative process, and other tumors as well. Ultimately landing to have a short life span. Our patient did not have any CNS abnormalities. Further neurodegenerative problems that arise include impaired cognitive ability, ineptitude to walk, hearing loss, delayed sexual development, abnormal speech, and inability to swallow leading to the requirement of a feeding gastrostomy. Our patient did not have any impaired cognitive abnormalities; however, he had difficulty walking. Studies also propose that below 20 years, XP patients have an increased risk for brain cancers and those at other CNS locations. The Peculiarity of XP is related to young-onset and lesion which commence around 2-8 years. To diagnose XP, DNA analysis is often used helping to differentiate XP from autosomal dominant diseases that could be mistaken for XP including Peutz-Jeghers syndrome, Cockayne syndrome, Leopard syndrome, and Carney complex. In our patient, we could not do genetic analysis due to financial restrictions. The most common fate for individuals with XP is death from skin cancer, most frequently due to metastatic melanoma or invasive squamous cell carcinoma. Patients with XP are 1000 times more prone to skin cancers caused by UV irradiation.

Xeroderma pigmentosum can occasionally also affect the respiratory system in the form of an ILD. The underlying pathogenic mechanism behind this development is based on short telomere abnormality. This triggers an inflammatory state and precipitates ILD in such individuals on exposure to infection or hypersensitivity. Patients diagnosed with ILD usually have symptoms of cough or dyspnea on exertion; for many, there is evidence of pulmonary restriction, decreased diffusion capacity, and radiographic appearance of alveolar and/or reticulonodular infiltrates. The onset of respiratory symptoms can be in childhood or they could be noticed in early adulthood like in our case. The XPILD is peculiar in its histology, which is uniquely characterized by chronic inflammation and lung fibrosis. In our case, as the patient is very symptomatic, TBLB was not done and as signs and symptoms are non-specific, the clinical examination usually does not contribute to the diagnosis of ILD. On pulmonary function testing, restrictive lung disease may express the presence of an interstitial process. In our patient, pulmonary function test showed a restrictive pattern with FVC of 9% and IP of 10%. Knowledge of its existence is pertinent to maintain a high index of suspicion for unearthing its diagnosis in such rare syndromes. This helps to attain a definitive diagnosis by a multidisciplinary approach and avoid unnecessary invasive investigations like a lung biopsy.

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