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Ataxia-telangiectasia

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A 20 - year-old schoolteacher presented to her GP with the recurrent dystonic movement of the left arm, loss of appetite and weight loss of 6 kilograms in the last three months. She started to feel unstable on her feet and had near fallen. She did not smoke or drink alcohol. Her past medical history was non-contributory. She was not on any regular medication including over counter medications. There was no significant family history.

She traveled to India a year before. She spent six months on a mission and enjoyed food and drinks from the hotel. She was well with no symptoms during her trip. She was UpToDate with her immunization.

A General Practitioner (GP) performed the examination which was unremarkable apart from the dystonic movement of the left arm. Following the consultation with a General Physician, the GP arranged the following blood tests which included Full Blood Count, Erythrocyte Sedimentation rate (ESR), C- reactive protein (CRP), Liver Function Tests(LFT), Renal Function Tests, serologies for hepatitis A, B, C, D, E, serum ceruloplasmin, alpha-fetoprotein, Antinuclear antibodies (ANA) double-stranded (ds) DNA, C3 and C4 complement levels, serum iron, serum B12 and Folate levels, serum Zinc, homocysteine, methylmalonic acid, tumor markers, carbohydrate-deficient transferrin, albumin creatinine ratio, vasculitis screen, 24-hour Urinary Copper, Whole- body Computed Tomography (CT) screening and mammogram. The investigations showed MCV of 78 fl(femtoliter), ESR of 40 mm/hr, CRP of 100(mg/L) with an elevation of CA 19-9. Serum alpha-fetoprotein was highly elevated at 200ng/ml. Computed tomography (CT) scan of the head confirmed cerebellar atrophy and a Mammogram raised a concern of Breast mass. Bronchiectasis was found on the CT scan of the chest and a liver mass was showed on the CT of the abdomen.

The patient was admitted to a hospital for multidisciplinary assessment including a neurologist, an oncologist, and a pulmonologist. She was seen by a neurologist. A high-resolution magnetic resonance image (MRI) in conjunction with diffusion-weighted imaging showed cerebellar atrophy and MR spectroscopy was unremarkable. Cerebrospinal fluid (CSF) findings including opening pressure, microscopy and biochemistry were normal. Protein 14-3-3 was not detected.

The patient was treated with levodopa which aborted dystonia. She was reviewed by an oncologist who arranged MR of the breast which showed an enhancing mass in the lower quadrant right breast. She underwent a Core Biopsy which confirmed duct carcinoma in situ (DCIS). The BRAC1 and BRAC2 were not detected and molecular analysis showed that the tumor was ER-negative (estrogen receptors), PR-negative (progesterone receptor (PR) and HER-2(human epidermal growth factor receptor-type2) negative. Tumor markers showed an elevation of CA 19-9 with normal carcinoembryonic antigen (CEA) and CA 125 levels. A PET scan did not show any abnormal FDG uptake. The patient was seen by a hepatologist who arranged for a repeat workup for Wilson disease and hemochromatosis, FibroScan and MRI of the liver. No abnormal findings in serum ceruloplasmin, 24-hour urinary copper, genetic tests for Wilson disease, serum iron, ferritin, transferrin saturation, C282Y / H63D, and HFE genotyping. FibroScan evaluation measured a liver stiffness of 2 kPA (The normal range for a fibroScan is between 2 kPA to 7kPa). An abdominal MRI and a triphasic CT of the liver confirmed a mass in segment 11 measuring 5 cm with no evidence of cirrhosis of the liver.

A fine-needle aspiration biopsy of the liver was performed and cytology revealed a hepatoma with no evidence of cirrhosis of the liver. Upper and lower GI endoscopies were all normal and endoscopic ultrasound with multiple Bruch biopsies ruled out pancreatic or biliary malignancies.

The patient was then referred to a hepatobiliary surgeon and a breast oncologist. The patient underwent liver resection, partial mastectomy, and neoadjuvant chemotherapy. Her surgeries were uneventful with no major postoperative complications. However, she developed a severe cough with daily production of mucopurulent sputum and hypoxemia requiring high-flow oxygen therapy, two weeks course of broad-spectrum antibiotics in addition to extensive chest physiotherapy and immunoglobulin infusion. A CT of the chest and CTA showed hypoplastic thymus and active bronchiectasis. A pulmonary function test revealed mild obstruction with no evidence of emphysema or increased lung volume. Diagnostic workup did not reveal an underlying cause of bronchiectasis and bacterial, viral, fungal and mycobacterial cultures and PCR were negative. However, IgA level was undetectable with a low lymphocytic count, low CD4, low CD8 and low B cell count. CT sinus and neck were normal.

She was started on intravenous immunoglobulin (IVIG) and regular follow-up with an immunologist was arranged. Also, the patient was advised that blood products should be washed before transfusion to avoid anaphylactic reaction since severe anaphylactic or allergic reactions may occur during blood transfusion due to IgA deficiency. She was assessed by a speech therapist who advised for videofluoroscopy which showed oropharyngeal dysphagia and gastroesophageal reflux. He has been identified as a high-risk patient for aspiration. The patient was advised to continue chest physiotherapy as an outpatient.

The patient was readmitted to the hospital for NG feeding with close monitoring for refeeding syndrome. She showed some improvement and gained weight. Her regular blood tests were unremarkable apart

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from a low MCV which was likely due to elevated HbA2 level. She had a fall on the ward and witnesses to the fall reported that the patient did not lose consciousness and did not have any injuries. She was assessed by a physiotherapist who reported that the patient had an ataxic gait. The closing of her both eyes did not cause a worsening of her coordination and her reflexes were weak.

She was examined by a neurologist and noted to have severe cerebellar ataxia, bilateral telangiectasia in the bulbar conjunctiva, sclera and the back of her chest. Examination of the cranial nerves revealed nystagmus on lateral gaze, oculomotor apraxia with impaired visual fixation, hypsometric saccadic and pursuit eye movements.

The patient was counseled by a geneticist for genetic testing to confirm the diagnosis of ataxia-telangiectasia(A-T). She underwent genetic testing which confirmed the mutated Ataxia telangiectasia gene (A-M gene). Cultured lymphocytes showed a moderate amount of functioning protein kinase. The diagnosis of Ataxia-telangiectasia was confirmed clinically and genetically.

Discussion

Ataxia-telangiectasia is an autosomal recessive neurodegenerative disease that varied in severity. The severe disease usually manifests early and most of the patients will be wheelchair-bound by the age of 15 [1]. The main manifestation is recurrent falls early in life due to cerebellar ataxia and peripheral sensory-motor neuropathy [2]. Neurodegeneration is not only confined to the cerebellum and other structures of the brain can be affected in the degenerative process. Neuroimaging usually shows atrophy of the cerebellar vermis, Purkinje cells, cerebellar hemispheres, cerebrum, brain stem and spinal cord might be involved [3]. The milder forms of the disease usually manifest at the age of 20 or older due to the presence of atypical mutation where the protein kinase activity is preserved. The prevalence of Ataxia-telangiectasia is 1 in 40 000 to 100 000 [4]. and A-T is usually underdiagnosed in resource-limited countries due to the limited availability of genetic testing to confirm the diagnosis of A-T [5]. Ataxia telangiectasia is common in sub-Saharan Africa due to consanguinity [6].

Ataxia Telangiectasia is an autosomal recessive disease due to biallelic mutation of the ATM gene causing loss of kinase activity even if the protein is expressed. Milder forms are associated with the expression of ATM activity. In classic typical cases, patients present with incoordination due to cerebral ataxia and do not have the classic wide base gait due to concomitant seismometer peripheral neuropathy.

Telangiectasia in most patients occurs in the palpebral conjunctiva and the absence of telangiectasia does not rule out the diagnosis. Telangiectasia could occur in the brain, spinal cord [7]. It is neither itchy nor painful. Other manifestations of ataxia-telangiectasia include recurrent sinopulmonary infections causing bronchiectasis, recurrent micro and macro aspirations due to pharyngeal dysphagia and poor mucociliary clearance, bulbar muscles weakness and hemoglobinemia. Restrictive lung disease is common due to respiratory weakness, and impaired coordination of respiratory muscles.

Patients with ataxia-telangiectasia are usually sensitive to radiotherapy and radiomimetic chemotherapy. These patients should not be exposed to radiotherapy or radiomimetic unless the benefits outweigh the risks. An MRI is replacing a CT as a tool of investigation [8].

Examination of eyes usually reveals gaze-evoked nystagmus, strabismus, oculomotor apraxia, hypsometric saccades and pursuit movements. Patients with ataxia-telangiectasia usually die either from infections or cancers. The common malignancies are lymphoma, leukemia and breast cancer. The carriers of ATM have a higher chance of developing breast cancer. Therefore, regular surveillance with biannual breast examination and annual MRI is recommended [9]. Orthopedic manifestations are scoliosis and feet deformity [10] and other manifestations include premature aging with gray hair, delayed puberty, gonadal dysgenesis, hyperkinetic movement disorders such as chorea, dystonia, and athetosis [11], insulin-resistant diabetes and loss of weight as a result of pharyngeal dysphagia and weakening of the bulbar muscles. Patients with low body mass index should be considered for a gastrostomy tube in addition to oral feeding.

Ataxia-telangiectasia is a multisystem degenerative disease and it is a progressive disease. The management and treatment of A-T is symptomatic and supportive. Although there is no cure, early diagnosis even in poor resources countries is critical as it may significantly alter the overall prognosis. Any neurological disease at a young age with telangiectasia should be screened with blood tests such as alpha-fetoprotein and MRI of the brain. Patients with A-T should have multidisciplinary care with neurologists, movement disorder specialists, respiratory physicians, oncologists, general physicians with interest in ataxia-telangiectasia and geneticists.

The main differential diagnoses of ocular apraxia are cerebral palsy and congenital ocular motor apraxia. Cerebral palsy is usually a non-progressive disease and congenital ocular motor apraxia is characterized by delayed development of visual saccades which improves with time. Another important differential diagnosis is Friedreich Ataxia which presents with ataxia, the absence of tendon reflexes, cardiomyopathy and diabetes and does not present with telangiectasia, oculomotor apraxia and elevated alpha-fetoprotein [12].

In summary, ataxia-telangiectasia is an underdiagnosed neurodegenerative neurocutaneous disease with different genotype-phenotype patterns. Once the diagnosis of AT is confirmed, patients should continue surveillance for malignancies and family members should be offered genetic counseling to diagnose asymptomatic heterozygous carriers who will require indefinite surveillance for carcinoma of the breast.

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