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"Secondary Hypertrophic Osteoarthropathyin a patient with Neurofibromatosis Type-1- a case report"

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Abstract: We describe the case of a patient with Neurofibromatosis type 1 (NF1) and Secondary Hypertrophic Osteoarthropathy. On this association so far, hypertrophic osteoarthropathy seems to be related to the vascular involvement of Neurofibromatosis wherein some studies reveal release of PDGF (platelet derived growth factor) by the neural tumor.In order to exclude other causes of secondary Hypertrophic osteoarthropathy all possible causes were excluded.On the basis of clinical findings and exclusion of all other causes, and no literature or case reports suggestive of presence of Hypertrophic Osteoarthropathy in Neurofibromatosis type-1, this finding attains animportant clinching and rare clinical entity and also signifies to include one among the neurological causes of secondary Hypertrophic Osteoarthropathy. The possible pathophysiology of Hypertrophic Osteoarthropathy in patient with neurofibromatosis has been discussed.

Keywords: Neurofibromatosis Type 1, Hypertrophic Osteoarthropathy (HOA), Platelet derived growth factor (PDGF), café –au-lait spots

INTRODUCTION

VonRecklinhausen's disease or Neurofibromatosis type 1 (NF) is an autosomal dominant dysplasia of ectoderm and mesoderm with a variable clinical expression characterized by collections of neurofibromas, cafe´-au-lait spots and pigmented hamartomas in the iris (Lish nodules). NF has a prevalence of one in 3,000 and in 30–50% of cases there is nofamily history of the disease. These sporadic cases probably arise from (usually paternal) germ cell mutations [1].

In NF, the thorax and lungs can be affected inseveral ways: cutaneous and subcutaneous neurofibromason the chest wall; kyphoscoliosis; ribbon deformity of the ribs; thoracic neoplasms;and interstitial lung disease (ILD). Sporadiccases of NF with diffuse lung disease (NF-DLD) have been published in case reports [2].

Digital clubbing is one of the oldest, yet poorly understood, signs in clinical medicine. The bulbous deformity of the digits results from edema and excessive collagen deposition. The small blood vessels in the digits are dilated and have thickened walls. The number of arteriovenous anastomoses is also increased.

Digital clubbing/Hypertrophic steoarthropathy is classified into:

Primary

- Idiopathic
- hereditary i.e., Touraine-Solente-Gole syndrome and

Secondary

- Cardiac-SBE and Fallots tetralogy (clubbing with cyanosis)
- Respiratory-bronchogenic ca (squamous cell type), suppurative (bronchiectasis, lung abscessandempyema), ILD and mesothelioma
- Biliary cirrhosis
- IBD (inflammatory bowel disease)

Grades of clubbing: 1. Fluctuation is positive due to increased proliferation of cells at nail base with obliteration of onychodermal angle. 2. Grade 1 + increasd AP and transverse diameters of nails. 3. Grade 2 + increase in pulp tissue resulting in Parrot's beak or drumstick appearance. 4. Grade 3+ Hypertrophic osteoarthropathy [3].

It can be confirmed by observation of the Schamrothsign, determination of the digital index, or by calculationof the phalangeal depth ratio. As it may be a signof serious underlying disease, a comprehensive workupshould be performed when a patient presents withdigital clubbing [3].

Hypertrophic osteoarthropathy (HOA) is a clinical syndrome characterised by clubbing of digits, periosteal bone formation and arthritis. Clubbing is an invariable feature of HOA but can also occur as an isolated manifestation. It is now believed that isolated clubbing represents either an early stage or one element in the spectrum of HOA.The pathogenesis of HOA is not known [4].

CASE REPORT

A 45 year old male, Mr. X married, farmer by occupation had presented with history of fever for 2 days, mild to moderate degree, associated with mild joint pain in the fingers and toe joints. His general physical examination was normal. Pulse rate: 80 beats per minute, regular, normal in volume and character, blood pressure: 126/70 mmHg. Systemic examination of the cardiovascular system, respiratory system and per abdomen examination didn't show any suggestive findings. Neurological examination revealed multiple neurofibromas over the arms, forearms and trunk and presence of neurocutaneous markers such as café-au-lait spots.

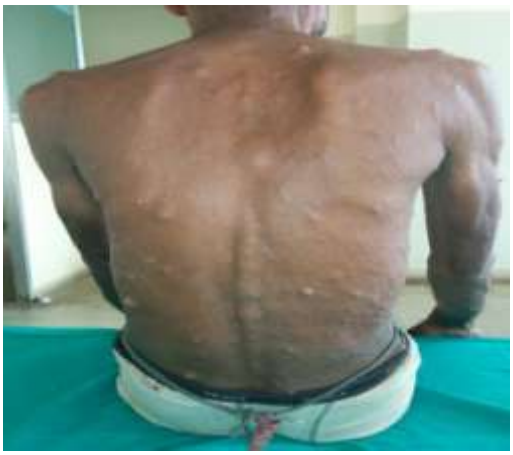

Fig-1

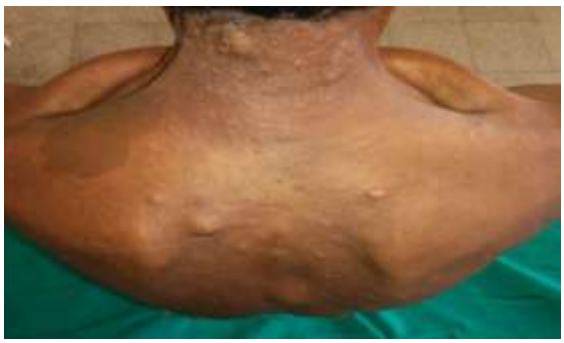

Fig-2

There was no presence of lisch nodules in iris and neurological examination didn't reveal any focal neurological deficit. Local examination of joints revealed Grade 3+ clubbing of fingers in the upper limbs and toes in the lower limbs suggestive of hypertrophic osteoarthropthy.There was no joint tenderness. There was no family history of similar complaints.Evaluation for fever didn't reveal any foci of infection

Fig-3

A diagnosis of Neurofibromatosis type-1 was made based on the examination findings. The presence of clubbing was perplexing and search for secondary causes of hypertrophic osteoarthropathy was investigated. Hematologicalinvestigations revealed normal haemogram, renal function tests, liver function tests and thyroid profile were well within normal limits. Imaging- chestX ray was normal and didn't reveal any infective or malignant lesions, 2D Echocardiography didn't reveal any cyanotic lesions or any lesions of infective endocarditis. Ultrasound scan of the abdomen didn't reveal any features suggestive of liver disease. Colonoscopy didn't reveal any features suggestive of ulcerative colitis or crohn's disease. X ray of hands revealed swelling of soft tissue of the terminal fingers and toes.

A diagnosis of hypertrophic osteoarthropathy secondary to Neurofibrosis type-1 was made. Patient was conservatively treated with antipyretics and analgesics and patient recovered in a duration of 3-4 days.

DISCUSSION

We report the case of a patient with neurofibromatosis-type 1 and hypertrophic osteoarthropathy. Only cases of hypertrophic osteoarthropathy in von Recklinghausen's disease have been reported so far in the presence of inflammatory bowel disease and in the presence of pulmonary arterial hypertension. [5, 6]

In all reports clubbing seems to be related to the vascular involvement of neurofibromatosis and it causing secondary systemic manifestations and henceforth causing hypertrophic osteoarthropathy; although histology was described only in one case.

In our patient all the conditions associated withSecondary hypertrophic osteoarthropathysuch as connective tissue diseases, chronic lung disease, congenital or acquired heart diseases, HIV infection, drug and toxins, hemoglobinopathies, myeloproliferativedisorders, thromboembolism were excluded.

If we go into the literature of causes and theories of hypertrophic osteoarthropathy; two theories traditionally put forward to explain HOA are:

- Neurogenic theory
- Humoral theory

The neurogenic theory proposes that a neural reflex initiated by vagal stimulation from the site of disease leads to vasodilatation and other features of HOA. This is supported by the fact that the disorders associated with HOA involve sites innervated by the vagus nerve.

The humoral theory6 postulates that mediators responsible for HOA are humoral and normally present in the venous circulation. These are ordinarily inactivated by the lung. In conditions like cyanotic congenital heart disease these mediators escape filtration/inactivation by the lungs.

However, recent studies suggest that platelets play an important role in the development of HOA.

The circulating megakaryocytes and large platelet particles present in the venous circulation normally break up in the pulmonary vascular bed, macrothrombocytesreach distal extremity sites where they interact with endothelial cells resulting in release of platelet derived growth factor (PDGF) and fibroblast growth factor(s) thus inducing acropachy.

Stimulation of fibroblasts by PDGF and transforming growth factor beta results in cell growth and collagen synthesis [7, 8].

Some genetic studies have revealed a very important finding wherein PDGF-A gene transcription is governed by interplay between NF1/X and Sp1. Henceforth Neurofibromatosis type -1 has altered and varied expression for transcription and production of PDGF-A chains in the molecule. [9]

The presence of hypertrophic osteoarthropathy in our case may be postulated in view of presence of neurofibromatosis type -1 and possible expression of PDGF and concomitant vascular mediated clubbing of fingers and toes. This could be the only possible inter-relation between these two conditions can be discussed as of now.

Further genetic, molecular and histological studies are required to substantiate possible pathophysiology of Neurofibromatosis type-1 and hypertrophic osteoarthropathy.

The treatment of secondary HOA is to treat the underlying cause. Removal of lung cancer, correction of cardiac malformation, and successful treatment of bacterial endocarditis may lead to a reversal of the clinical features.

In conclusion, HOA is a syndrome characterized by abnormal proliferation of skin and osseous tissue at the distal extremities. The presence of bone pains with joint pains in a patient with clubbing should alert a clinician to the possibility of HOA. Treatment is directed towards removal of underlying cause, if any, and symptom relief.

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