*Indian Journal of Medical Case Reports ISSN: 2319–3832(Online)*
*An Open Access, Online International Journal Available at http://www.cibtech.org/jcr.htm*
*2017 Vol.6 (1) January-March, pp. 1-5/Mahajan et al.*

***Case Report***

# SEVERE PULMONARY ARTERY HYPERTENSION IN A PATIENT OF NEUROFIBROMATOSIS-1: A RARE ASSOCIATION

***Kunal Mahajan, Sanjeev Asotra, Rajeev Merwaha, Sanjay Rathour, Davinder Pal Singh and Prince Kumar Paul**
*Department of Cardiology IGMC Shimla India*
**Author for Correspondence*

## ABSTRACT
Neurofibromastosis-1 has been classified as a cause of pulmonary artery hypertension by WHO in its latest guidelines. However, the mechanism of this association is still not clear. There is paucity of data on NF-1 associated PAH. Less than 15 cases have been described in literature so far. The authors report a case of a 37 year old female presenting with exertional dyspnea who was also having skin lesions characteristic of NF-1. She was found to have severe PAH and after excluding all possible etiologies, NF-1 associated vasculopathy was kept as the probable diagnosis. This disease association has a poor outcome and its awareness among physicians would enable early identification and improve management.

***Keywords:*** *Neurofibromatosis-1, Pulmonary Artery Hypertension, Vasculopathy*

## INTRODUCTION
NF-1 is an autosomal dominant genetic disorder with an incidence of approximately 1 in 3000 individuals (Lammert *et al.,* 2005). Approximately one-half of the cases are familial; the remainder are new mutations (North, 1993). It is a multisystem disorder that is characterized by cutaneous findings, most notablycafé-au-lait spots and axillary freckling, by skeletal dysplasias, and by the growth of both benign and malignant nervous system tumors, most commonly benign neurofibromas. Although, infrequent, arterial vasculopathies are well-recognised complications of this disease and one of the most important causes of early death in persons with NF-1 (Jett and Friedman, 2010). Pulmonary artery hypertension is a very rare complication of NF-1 and is thought to be secondary to vasculopathy (Stewart *et al.*, 2007). The most recent guidelines of pulmonary artery hypertension classification (Nice, France 2013) have include NF-1 as a cause of PAH in a group with unclear and/or multi factorial mechanisms (Simonneau *et al.,* 2013). We presenta case of NF-1 presenting with exertional dyspnea and ultimately diagnosed to have pulmonary hypertension. Awareness of such an association would allow early identification and better management of similar cases.

## CASES
A 37 years old female presented to us with complaints of class III exertional dyspnea of 2 years duration which was gradually progressive. It was associated with fatigue, palpitations, swelling feet and anorexia. She was mother of two children with normal deliveries at home .We found her to have skin lesions which were undiagnosed previously. She was having multiple café-au-lait spots, inguinal freckles and cutaneous neurofibromas [figure 1]. Lisch nodules were seen on slit lamp examination [figure 2]. We diagnosed her to have Neurofibromatosis-1 and begin evaluation for the cause of her dyspnea. She was in WHO class III breathlessness and developed tachypnea and tachycardia even at mildest physical activity. Her blood pressure was 104/70 mm Hg. Cyanosis and clubbing were absent. Pedal edema was present. Her lung sounds were normal, but she had an accentuated second heart sound in the second left intercostal space, grade III left parasternal heave and a systolic murmur of Tricuspid regurgitation. Electrocardiogram revealed right axis deviation with right atrial and ventricular enlargement [figure 3] Chest X-ray showed anenlarged right and left pulmonary artery with peripheral pruning and enlarged right heart chambers [figure 4]. Echo cardiography revealed dilatation of the right atrium and ventricle, severe pulmonary artery hypertension and moderate (grade II) tricuspid insufficiency. Left heart diseases and congenital heart diseases were excluded. Cardiac catheterization confirmed the diagnosis of severe PAH with

elevated mean pulmonary artery pressure (51 mm Hg, 75/35 mm Hg), normal pulmonary capillary wedge pressure (11 mm Hg), and high pulmonary vascular resistance (19.7 wood units). Vasoreactivity test was negative. Work up for cause of pulmonary artery hypertension revealed a negative serology for collagen vascular disorders, APLA and HIV. Thyroid and liver function tests were normal. Complete hemogram revealed no evidence of hemolysis. USG liver and portal system showed normal study. Pulmonary function tests revealed a normal lung volume with no signs of pulmonary obstruction. Chest CT revealed no parenchymal lung disease and CT pulmonary angiography revealed no evidence of CTEPH. Unfortunately, genetic testing for neurofibromatosis type 1 and pulmonary hypertension/bone morphogenetic protein receptor 2 and others were not available. CT head was done which revealed sphenoid dysplasia that further supported our diagnosis of neurofibromatosis. Patient had a family history of similar skin lesions in her father, brother and sister but none of them complained of dyspnea. On 6 min walk test, she covered 350m. Her serum BNP levels were elevated (350 pg/ml). Patient was started on diuretics, phosphodiesterase inhibitors and anticoagulants and would be monitored closely on follow up.

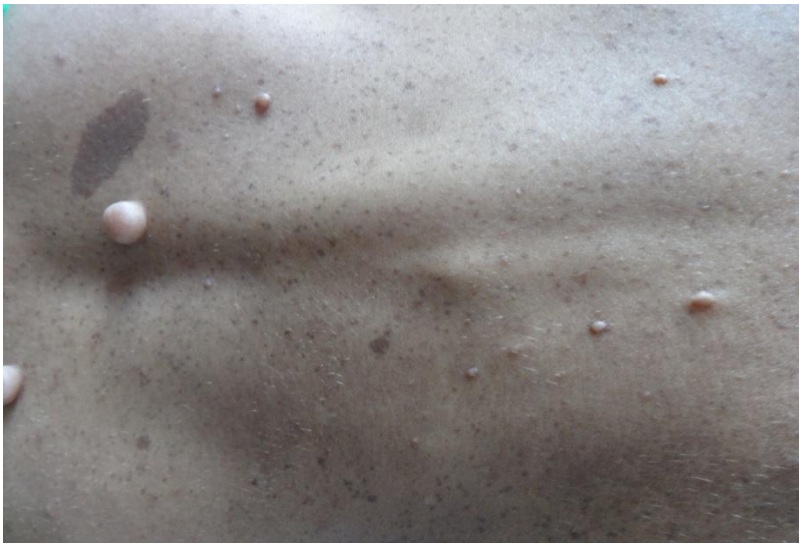

**Figure 1: Showing Café-au-lait Spots and Cutaneous Neurofibromas**

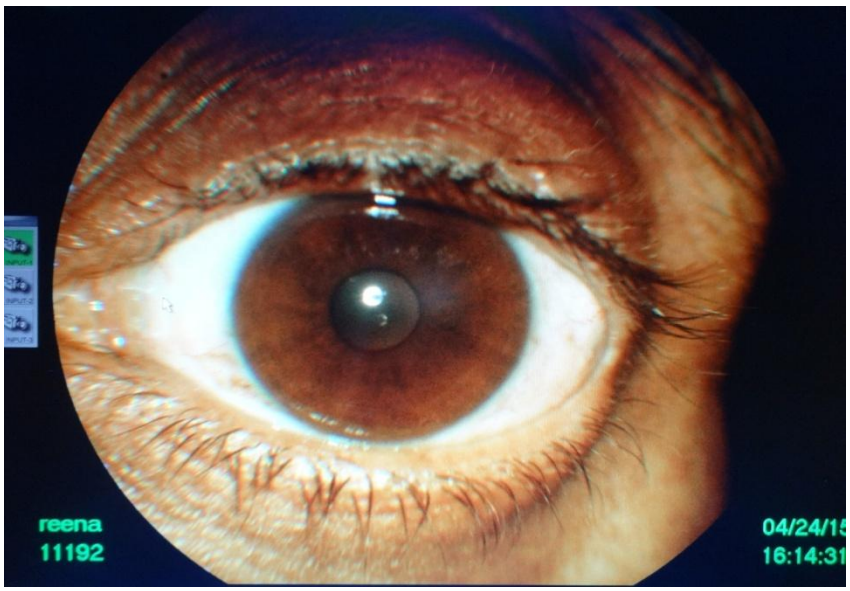


**Figure 2: Slit Lamp Examination Showing Lisch Noduleson Iris near Superior Limbic Margin**

***Case Report***

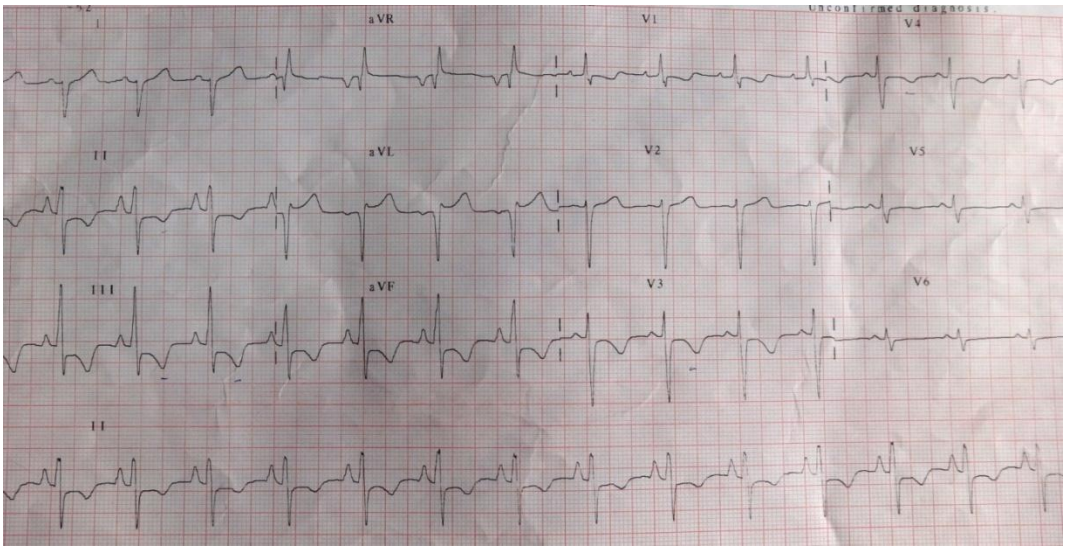


**Figure 3: ECG Showing Right Axis Deviation with Right Atrial and Ventricular Hypertrophy**

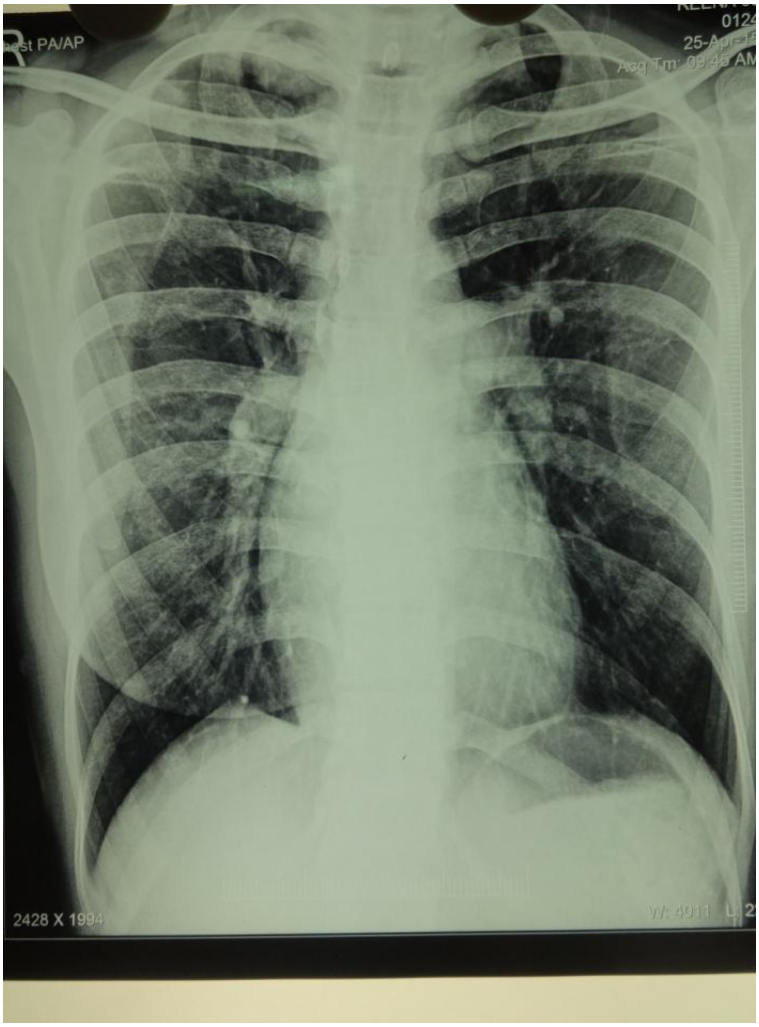


**Figure 4: Chest X-ray Showing Enlarged Right Sided Chambers and Dilated Right and Left Pulmonary Artery with Peripheral Pruning**

## DISCUSSION

Neurofibromatosis type 1 (NF-1) is a multisystem genetic disorder that commonly is associated with cutaneous, neurologic, and orthopedic manifestations. It is a common (1 per 3,000 individuals) monogenic disorder and inherited in an autosomal-dominant pattern. The manifestations of NF-1 result from a mutation in or deletion of the NF-1 gene. The gene product neurofibromin serves as a tumor suppressor; decreased production of this protein results in the myriad of clinical features.

The 7 clinical criteria used to diagnose NF-1 are as follows:

- Six or more café-au-lait spots or hyper pigmented macules greater than or equal to 5 mm in diameter in prepubertal children and 15 mm post pubertal
- Axillary or inguinal freckles (>2)
- Two or more typical neurofibromas or one plexiform neurofibroma
- Optic nerve glioma
- Two or more iris hamartomas (Lisch nodules), often identified only through slit-lamp examination by an ophthalmologist
- Sphenoid dysplasia or typical long-bone abnormalities such as pseudarthrosis
- First-degree relative (eg, mother, father, sister, brother) with NF-1 (Gutmann *et al.*, 1997)

Our patient met 6 out of these 7 criteria.

Complications of NF-1 can include visual loss secondary to optic nerve gliomas, spinal cord tumors, scoliosis, vascular lesions, and long-bone abnormalities.

Neurofibromin, the NF1 gen-encoded protein, has a role in both tumour suppression and regulation of cell growth and proliferation (Friedman *et al.*, 2002; Ferner, 2007). Since neurofibromin is expressed in endothelial and smooth muscle cells of blood vessels, (Stewart *et al.*, 2007; Friedman *et al.*, 2002) it has been hypothesised that its deficient function could originate a vasculopathy by impairing the response of these cells to growth suppressor signals.

Little is known about the frequency, pathogenesis, and natural history of NF1-associated vasculopathies. They primarily affect the renal, cerebral, and peripheral vascular beds, and appear to contribute to the excess mortality of children and young adults with NF-1 (Hamilton and Friedman, 2000). NF1-associated vasculopathies are heterogeneous and affect a variety of arteries of different sizes throughout the body. Liecategorized NF1-associated vasculopathies as (1) intimal vascular smooth muscle cell proliferation in large elastic arteries, (2) intimal vascular smooth muscle cell proliferation with fibrosis and neoangiogenesis in medium-sized elastic arteries, or (3) plexiform (or angiomatoid) intimal proliferation in small arteries and arterioles (Lie, 1998). The observed clinical and pathologic heterogeneity of NF1-associated vasculopathies probably reflects heterogeneity of underlying pathogenetic mechanisms. Stewart *et al.*, (2007) used autopsy specimens of the patients with NF-1 PAH to demonstrate that pulmonary vasculature is also among the arterial beds affected by NF-1 vasculopathy. NF-1 associated PAH is a rare identity. Although, WHO in its latest classification of PAH (Simonneau *et al.*, 2013) has included NF-1 as a cause in the group of diseases with unclear/multifactorial mechanisms. Less than 15 cases have been described in literature prior to this case (Porterfield *et al.*, 1986; Samuels *et al.*, 1999). In the previous cases, like in ours, extensive workup revealed no evidence of diseases or findings to explain PAH other than NF-1 itself.

Despite the paucity of data, the prognosis of this association between these two disease identities is dismal (Stewart *et al.*, 2007). Even in the era of PAH-specific therapies, 1-, 2-, and 3-year survival rates of patients with PAH is 85.7%, 69,5%, and 54.9% for incident cases (Humbert *et al.*, 2010). Prognosis is similar if not worse in patients of NF-1 associated PAH (Stewart *et al.*, 2007).

The bone morphogenic protein receptor 2 (BMPR2) gene is mutated in 70% of patients with familial PAH and 20–25% of patients with idiopathic PAH (Machado *et al.*, 2009). BMPR2 gene analysis is very important to exclude a heritable or idiopathic PAH when the familial history of the patient is unsure. However, as per the data available BMPR mutation has been tested in 1/3$^{rd}$ patients of NF-1 associated PAH and no mutations or rearrangements were found in them. We did not perform BMPR2 gene testing in the present case but the patient had no familial history suggestive of PAH.

***Case Report***

In our patient all the conditions associated with PAH such as chronic lung disease, connective tissue disorders, congenital or acquired heart diseases, haemolyticanemia, liver diseases, HIV, CTEPH were excluded. Vasculopathy associated with NF-1 was the most probable cause in our case.

***Conclusion***

This case highlights the need of increased awareness among physicians regarding the association between NF-1 and PAH. Because of very low incidence of PAH, routine screening of all NF-1 patients for presence of PAH would not be recommended. However, if a patient of NF-1 develops dyspnea, fatigue or syncope, associated PAH should be immediately investigated.

***Abbreviations Used***

NF-1: Neurofibromatosis-1
PAH: Pulmonary Artery Hypertension
CTEPH: Chronic Thrombo Embolic Pulmonary Hypertension
BMPR2: Bone Morphogenic Protein Receptor 2
HIV: Human Immunodeficiency Virus
APLA: Anti Phospho Lipid Antibody
WHO: World Health Organisation
CT: Computerised Tomography

**REFERENCES**

**Ferner RE (2007).** Neurofibromatosis 1 and neurofibromatosis 2: a twenty first century perspective. *The Lancet Neurology* **6** 340–51.

**Friedman JM, Arbiser J, Epstein JA *et al.*, (2002).** Cardiovascular disease in neurofibromatosis 1: report of the NF1 cardiovascular task force. *Genetics in Medicine* **4** 105–11.

**Gutmann DH, Aylsworth A, Carey JC *et al.*, (1997).** The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. *The Journal of the American Medical Association JAMA* **278** 51-7.

**Hamilton SJ and Friedman JM (2000).** Insights into the pathogenesis of neurofibromatosis 1 vasculopathy. *Clinical Genetics* **58** 341-4.

**Humbert M, Sitbon O, Chaouat A *et al.*, (2010).** Survival in patients with idiopathic, familial and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation* **122** 156.

**Jett K and Friedman JM (2010).** Clinical and genetic aspects of neurofibromatosis 1. *Genetics in Medicine* **12** 1–11.

**Lammert M, Friedman JM, Kluwe L and Mautner VF (2005).** Prevalence of neurofibromatosis 1 in German children at elementary school enrollment. *Archives of Dermatology* **141** 71.

**Lie JT (1998).** Vasculopathies of neurofibromatosis type 1 (von Recklinghausen disease). *Cardiovascular Pathology* **7** 97-108.

**Machado RD, Eickelberg O, Elliott CG *et al.*, (2009).** Genetics and genomics of pulmonary arterial hypertension. *Journal of the American College of Cardiology* **54**(1 Suppl) S32–42.

**North K (1993).** Neurofibromatosis type 1: review of the first 200 patients in an Australian clinic. *Journal of Child Neurology* **8** 395.

**Porterfield JK, Pyeritz RE and Traill TA (1986).** Brief clinical report: pulmonary hypertension and interstitial fibrosis in von Recklinghausen neurofibromatosis. *American Journal of Medical Genetics* **25**(3) 531-5.

**Samuels N, Berkman N, Milgalter E *et al.*, (1999).** Pulmonary hypertension secondary to neurofibromatosis: intimal fibrosis versus thromboembolism. *Thorax* **54**(9) 858-9.

**Simonneau G, Gatzoulis MA, Adatia I *et al.*, (2013).** Updated clinical classification of pulmonary hypertension. *Journal of the American College of Cardiology* **62**(25 Suppl) D34-41.

**Stewart DR, Cogan JD, Kramer MR *et al.*, (2007).** Is pulmonary arterial hypertension in neurofibromatosis type 1 secondary to a plexogenicarteriopathy? *Chest* **132** 798–808.