CASE REPORT

Chronic eosinophilic pneumonia associated with neurofibromatosis type 1 : an unusual complication

Stamatis Katsenos[1,3], Melita Nikolopoulou[1], Efstathios Rallis[2], and Stavros H Constantopoulos[3]

[1]*Department of Pneumonology, and* [2]*Department of Dermatology, Army General Hospital of Athens, Athens, Greece ; and* [3]*Department of Pneumonology, University Hospital of Ioannina, Ioannina, Greece*

Abstract : Neurofibromatosis type 1 (formerly known as von Recklinghausen's disease) is an autosomal dominant disorder, which results from the proliferation of the neural crest cells, thus affecting any organ system. Several pulmonary manifestations have hitherto been reported, including chest wall deformities, diffuse lung disease, thoracic neoplasms, pulmonary arterial hypertension, central hypoventilation, diaphragmatic paralysis and meningocele. However, eosinophilic lung disorders have not been described. An unusual case of chronic eosinophilic pneumonia in a patient with neurofibromatosis type 1, is reported herein. He had a propitious outcome, following corticosteroid treatment. This is the first well-documented case of chronic eosinophilic pneumonia and neurofibromatosis type 1 in the same patient. These clinical entities might share common pathogenic mechanisms, as suggested by the present study, that could explain their co-existence. J. Med. Invest. 56 : 64-69, February, 2009

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INTRODUCTION

Neurofibromatosis type 1 (NF1), previously termed as von Recklinghausen's disease, is a common neurocutaneous condition with an autosomal dominant pattern of inheritance. Its birth incidence is approximately of one in 2500 and the minimum prevalence one in 4000-5000 (1). The disease has variable clinical expression and severity. Diverse associated complications have been described, involving any organ system and ranging from body and facial disfigurement, scoliosis and distinctive bony dysplasias with or without pseudoarthrosis and vasculopathies (cardiovascular and cerebrovascular diseases) to cognitive function impairment and malignant conditions (peripheral nerve sheath tumors, central nervous system gliomas, leukaemia, rhabdomyosarcoma and pheochromocytoma) (2).

In particular, NF1 affects the respiratory system in various ways : chest wall abnormalities (cutaneous and subcutaneous neurofibromas, kyphoscoliosis, rib notching from intercostal neurofibroma) ; primary thoracic or metastatic neural tumors ; interstitial fibrosis with bibasilar predominance with or without asymmetric upper lobe cystic and bullous disease ; pulmonary arterial hypertension, spontaneous massive haemothorax ; central alveolar hypoventilation ; bilateral diaphragmatic paralysis ; mediastinal involvement (lateral meningocele) (3-9).

Eosinophilic lung diseases have not so far been reported as associated complications of NF1. A case of chronic eosinophilic pneumonia in a patient with

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Address correspondence and reprint requests to Stamatis Katsenos, MD, 3, Ierarhou Panaretou St, 45445, Ioannina, Greece and Fax : +302651029432.

NF1 is described herein ; the patient recuperated with appropriate corticosteroid treatment.

CASE REPORT

A 25-year-old male non-smoker was referred to us because of dry cough and exertional breathlessness. The onset of symptoms dates from the previous four weeks with gradual worsening. His past medical history was unremarkable.

On physical examination, multiple café-au-lait macules (>6), oval with fairly smooth margins measuring 1.5 cm or greater in diameter, were distributed over the trunk and extremities (Figure 1). Freckles were also seen in both the axillary regions. On palpation, several firm subcutaneous papules scattered on the trunk were identified (Figure 1). A painful subcutaneous nodule on the right thigh was also detected. Chest auscultation showed sparse inspiratory squeaks throughout the upper and middle lung fields. The remainder of the clinical examination was unremarkable.

Basic laboratory tests were normal except for peripheral blood eosinophilia (2910 cells/μl), slightly increased erythrocyte sedimentation rate (25 mm/h), elevated serum C-reactive protein (9 mg/dl) and eosinophilic cationic protein (ECP) levels (196 μg/l). Arterial blood gases while breathing room air showed mild hypoxemia (PaO_2 : 70 mmHg, $PaCO_2$: 34 mmHg, pH : 7.44 and bicarbonate 24.5 mmol/l). Further investigations, which included antinuclear antibodies, C- and P-antineutrophilic cytoplasmatic antibodies, immunoglobulin levels, IgE antibody for specific allergens and serum complement analysis were unremarkable.

Skin tests for both *M. tuberculosis* and atypical mycobacteria were negative. Repetitive serologic tests and stool examination had no effect on the detection of parasites ova. Pulmonary function tests in conjunction with pulmonary diffusing capacity (single breath CO test) were within normal limits.

Chest X-ray revealed peripheral opacities in the left upper lung field, which represented alveolar consolidation (Figure 2). A high resolution chest computed tomography (HRCT) disclosed bilateral air space consolidations located in the periphery of the upper lobes as well as ground-glass opacities in the lingula (Figure 3a, b). A second chest X-ray, three days later demonstrated a nodular infiltrate in the right lower lung field with attenuation of left upper lung field opacities ; findings compatible with a migratory-like pattern.

The patient underwent fiberoptic bronchoscopy which showed only slight mucosal redness in the whole tracheobronchial tree. Bronchoalveolar lavage (BAL) was performed from the left upper lobe and lingula. BALF differential cell counts revealed 48% eosinophils, 32% alveolar macrophages, 16% lymphocytes and 3.8% neutrophils. All the microbiology

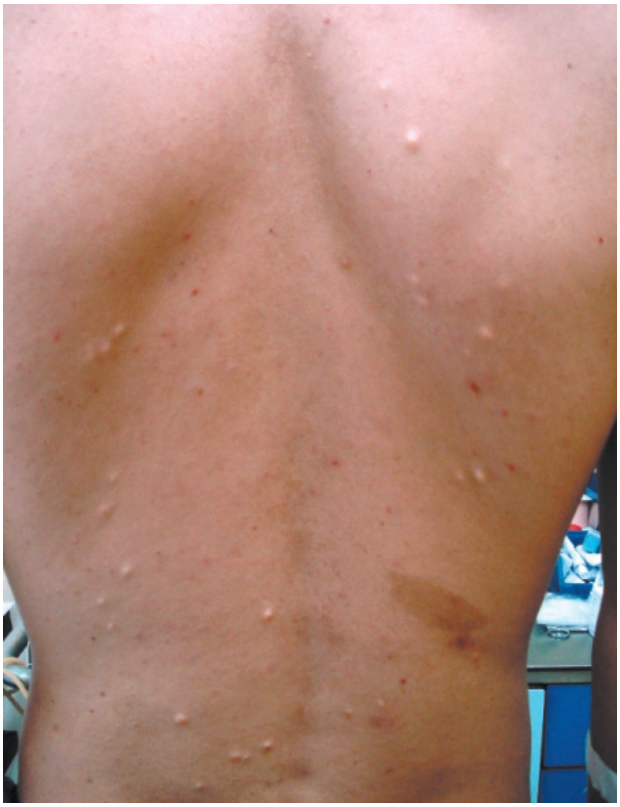

Figure 1. Café-au-lait spot and subcutaneous papules dispersed over the trunk.

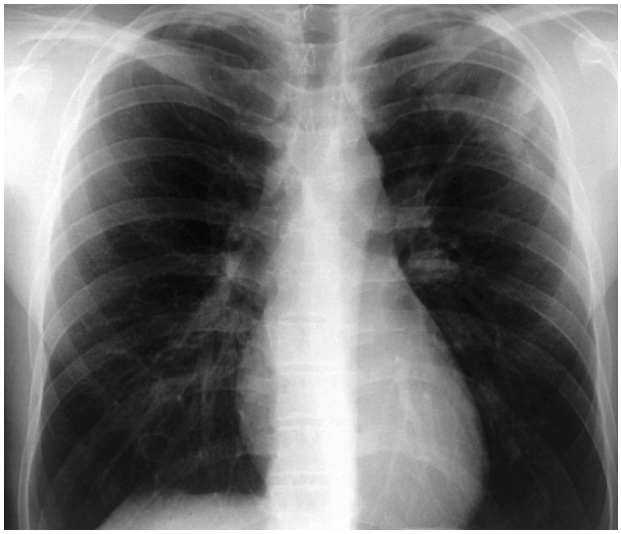

Figure 2. Chest radiograph showing peripheral alveolar opacities in the left upper lobe.

studies of BAL samples provided no evidence for bacterial, fungal or viral infection. Cytologic examination was also negative.

Bone marrow aspiration and biopsy were normal. Slit lamp examination revealed reddish brown spots within the lower pole of the irises, compatible with Lisch nodules (Figure 4). Excisional biopsy of the subcutaneous nodule on the right thigh was typical of neurofibroma. Additional work-up, including computed tomography of the abdomen, magnetic resonance imaging of the brain, long bones plain radiographs, as well as Doppler echocardiography disclosed no abnormalities.

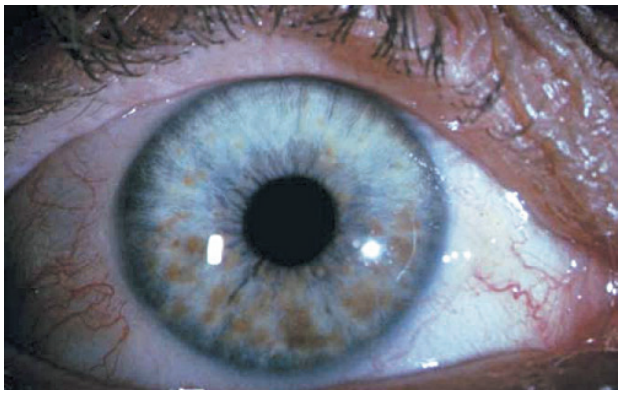

Figure 4. Lisch nodules.

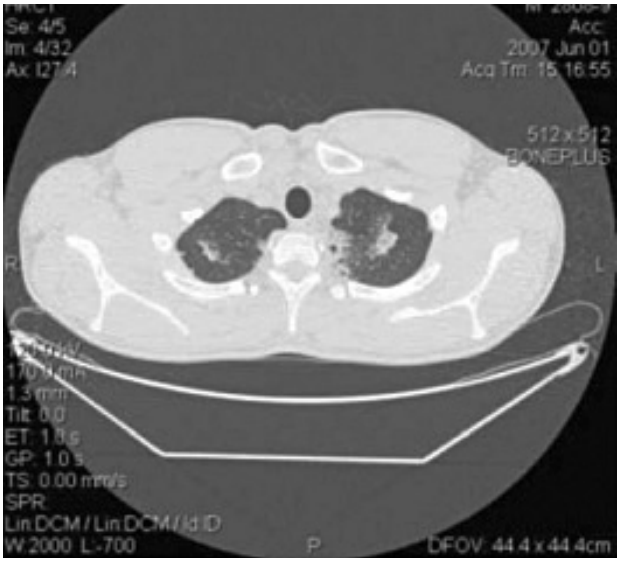

Figure 3a. High resolution chest computed tomography (HRCT) illustrating bilateral air space consolidations located in the periphery of the upper lobes.

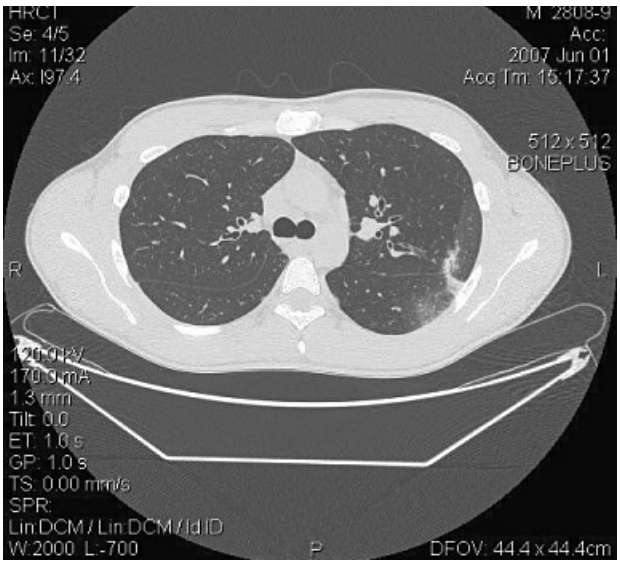

Figure 3b. HRCT depicts ground-glass opacities in the lingual.

The diagnosis of chronic eosinophilic pneumonia and NF1 was eventually established. The patient was started on prednisone 40 mg/day with rapid improvement of his clinical picture and chest imaging features normalization within two weeks. The initial prednisone dose was effectively tapered down over a period of several months, with a schedule of the steroid therapy completion in a year.

DISCUSSION

We report a case of a patient with known neurofibromatosis type 1 (NF1), who presented with chronic eosinophilic pneumonia, suggesting that NF1 may promote the development of chronic eosinophilic pneumonia.

NF1 is a comparatively common autosomal dominant neurocutaneous syndrome with a prevalence rate of about 1 per 4000-5000 (1). There is no family history of this disorder in approximately half of the patients, suggesting that spontaneous mutations are tangible. The gene liable for the NF1, called *NF1* gene, has been identified on chromosome 17q11.2. Its protein product, neurofibromin, is a negative regulator of cell proliferation and differentiation, functioning as a tumor suppressor (10). Although recent developments in molecular genetic testing confirm the diagnosis of NF1 in over 95% of patients, its diagnosis is still based mostly on published clinical criteria (11), (Table 1). In the present case, four major criteria were considered sufficient to support the diagnosis of NF1.

Chronic eosinophilic pneumonia is a distinct disease of unknown aetiology often accompanied by allergic diatheses, mainly asthma, which can antedate the condition by many years or can develop

Table 1. Diagnostic criteria for neurofibromatosis type 1 (NF1) (adapted from ref.11)

- Six or more café-au-lait spots>0.5 cm in prepubertal children and >1.5 cm in postpubertal individuals
- Axillary or inguinal freckling
- Two or more cutaneous neurofibromas
- One plexiform neurofibroma
- Two or more iris Lisch nodules
- An optic glioma
- A characteristic bony lesion (pseudarthrosis, hypoplasia of sphenoid wing, severe kyphoscoliosis)
- First degree relative with NF1

In order to make the diagnosis, at least two major criteria are required.

concurrently (12). Although firm diagnostic criteria are not available, the diagnosis can be derived from the combination of: (i) non-specific pulmonary symptoms (usually over two weeks duration), (ii) pulmonary opacities that are in most cases bilateral, peripheral and migratory, (iii) pronounced blood and/or alveolar eosinophilia (blood eosinophilic count>1000/mm^3, bronchoalveolar lavage eosinophilis>40%) and (iv) absence of any known cause of pulmonary eosinophilia (13). The hallmark of chronic eosinophilic pneumonia is a rapid and remarkable resolution of clinical, radiological and biological features with oral corticosteroids. In our patient this resolution occurred in two weeks.

Neurofibromatosis type 1 is an extremely variable condition in terms of its features occurrence and severity. Some afflicted patients have mild manifestations, whereas others experience more severe complications reducing life expectancy (1, 2). Mild cases may be missed, since affected individuals seldom seek medical attention. The present case was revealed by a compulsory physical examination as part of health evaluation for military service. The presenting respiratory symptoms, just before joining the army, forced our patient to ask further medical assistance, thus leading to the definite diagnosis.

A multitude of phenotypic features has been described in NF1, as virtually any organ can be affected by this neurocutaneous disorder. Especially, NF1 has a variety of manifestations in the thorax and lungs, as mentioned previously (3-9). Nevertheless, pulmonary eosinophilic disorders have not been reported to date in association with NF1. Search of the literature revealed only a report of NF1 complicated by acute lymphoblastic leukaemia (ALL) and hypereosinophilia (14).

The authors postulate that the occurrence of chronic eosinophilic pneumonia may be facilitated by neurofibromatosis type 1. It is firmly thought that nerve growth factor (NGF) plays a pivotal role in this relationship. Compelling circumstantial evidence suggests that NGF is involved in the pathogenesis of neurofibromatosis and its neurological complications (mainly neural tumors) (15-17). Indeed, high NGF plasma levels were detected in patients with NF1 (18).

However, several lines of evidence have also implicated NGF in the pathophysiology of various allergic diseases (19). Strictly speaking, NGF has been shown to interact with non-neuronal cells involved in innate and adaptive immune systems, such as lymphocytes, mast cells, macrophages, basophils and eosinophils themselves. Therefore, it intervenes in allergy-related immune cell functional activities, such as mast-cell degranulation, Th2 cytokine synthesis and release, antibody production from B cells and eosinophil survival (20).

Mast cells and eosinophils, the major key effector cells in allergic inflammation, are a source of NGF and influenced by it in their differentiation, survival and activation (21, 22). This mast cell-eosinophil cross-talk, through NGF and other specific preformed mediators, can perpetuate and even intensify allergic inflammatory process with possible development of tissue damage.

The magnitude of NGF involvement in the inflammatory stages of allergy has not only been shown in animal models or *in vitro* studies, but also in patients with allergic diseases and especially bronchial asthma, the best studied eosinophilic lung disorder. The expression of NGF is highly up-regulated and significantly correlated with the increased airways mast cells in asthmatic patients (23). Furthermore, enhanced NGF plasma and BAL levels are strongly correlated with atopy markers, disease severity and the development of bronchial hyperresponsiveness, suggesting that NGF mediates activation of bronchial eosinophils and substantially regulates eosinophilic inflammation in asthma (24). Similar immunopathogenic mechanisms have been observed in chronic eosinophilic pneumonia, lacking however any evidence on NGF involvement (12).

Recent studies in mice models demonstrate that *Nf1* deficiency results in increased numbers of immature and mature T cell subsets, as well as mast cells ; the latter ones might contribute to neurofibromas development through the release of several cytokines (10, 25). Antigenic stimulation may elicit T-lymphocytes and mast cells activation, which may be primed by *Nf1* gene mutations. As mentioned earlier, these cells are a source of NGF, which in

turn is the major key mediator that might orchestrate the eosinophilic airway inflammation, thus leading to the occurrence of chronic eosinophilic pneumonia (26). This immunological response could also be subserved by genetic factors that are hinted by a history of asthma and atopy in patient's brother.

Based on the aforementioned data concerning the role of NGF in NF1 and allergic inflammatory diseases, we measured NGF levels in the patient's serum and BAL using a highly sensitive NGF-specific two-site enzyme-linked immunosorbent assay (ELISA)-kit (Promega, Madison, WI, USA). Both NGF plasma and BAL levels were significantly increased (157 pg/ml and 235 pg/ml respectively with normal levels 3.8 ± 1.7 pg/ml and 53.9 ± 20.2 pg/ml). This may demonstrate a possible association among NF1, NGF and chronic eosinophilic pneumonia.

In conclusion, these observations suggest that chronic eosinophilic pneumonia could be included among potential pulmonary manifestations of NF1. Although a causal association between NF1 and chronic eosinophilic pneumonia cannot be explicitly ascertained from this descriptive study, we suggest that priming of specific immune cells by NF1 may generate chronic eosinophilic pneumonia, supported by further triggering factors (e.g. drugs, environmental exposure, bacterial and viral infections). These remarks may prompt studies on NGF involvement in chronic eosinophilic pneumonia.

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