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A 14-Year Diagnostic Delay of Neurofibromatosis Type 1 in a Patient with Hypertension and Leukemia: A Case Report

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Abstract

Background: Neurofibromatosis Type 1 (NF1) is an autosomal dominant neurocutaneous disorder. Renal complications include renovascular hypertension. We report a case diagnosed in a nephrology setting after a 14-year delay.

Case presentation: A 27-year-old woman with severe hypertension, acute myeloid leukemia (treated with bone marrow transplantation), and chronic graft-versus-host disease was admitted for acute pyelonephritis. Physical examination revealed multiple café-au-lait spots, axillary freckling, and cutaneous neurofibromas, leading to a clinical diagnosis of NF1 based on NIH criteria. Renal artery Doppler was normal. Renal function normalized after antibiotics and hydration.

Conclusion: This case highlights that NF1 can remain undiagnosed for years in patients with complex medical histories. A thorough physical examination by a nephrologist can identify NF1 and guide appropriate multidisciplinary surveillance.

Keywords: Neurofibromatosis Type 1, Von Recklinghausen Disease, Acute Kidney Injury, Pyelonephritis, Hypertension, Diagnostic Delay

1. Introduction

Neurofibromatosis Type 1 (NF1, Von Recklinghausen disease) is the most common phacomatosis, with an estimated incidence of 1 in 3,000 live births [1, 2]. It is an autosomal dominant disorder caused by mutations in the NF1 tumor suppressor gene on chromosome 17q11.2 [3, 4]. Clinical diagnosis is based on National Institutes of Health (NIH) criteria, which include café-au-lait macules, axillary or inguinal freckling, Lisch nodules, and neurofibromas [5, 6].

Although the diagnostic criteria are primarily cutaneous, NF1 has significant systemic manifestations, including renal complications. Renovascular disease, particularly renal artery stenosis, is the most common cause of secondary hypertension in NF1, but pheochromocytoma and aortic coarctation may also occur [7-10]. Consequently, a nephrologist may be the first to recognise NF1 in a patient presenting with early-onset or refractory hypertension. We report a case where NF1 was diagnosed in a nephrology unit after a 14-year diagnostic delay.

2. Case Presentation

A 27-year-old woman was admitted to our nephrology department for acute renal failure in the context of a febrile urinary tract infection. She was the product of a second-degree consanguineous marriage.

Her past medical history was notable for several conditions. She had presented with recurrent urinary tract infections caused by *Escherichia coli* despite prophylactic Bactrim therapy for more than five years. Hypertension had been diagnosed in adolescence and required quadruple therapy, including a calcium channel blocker (loxen 100 mg/day), a beta-blocker (sectral 100 mg/day), an angiotensin II receptor antagonist (aprovel 150 mg/day), and a centrally acting alpha-2 adrenergic agonist (aldomet 250 mg/day). At the age of 13, she was diagnosed with acute myeloid leukemia (AML), which was treated with chemotherapy followed by an allogeneic bone marrow transplant. At age 15, she developed chronic graft-versus-host disease (GVHD), manifesting as localized scleroderma and treated with corticosteroids. She also had epilepsy managed with sodium valproate (Depakine) and secondary amenorrhea since age 16.

Her family history revealed that her mother had a history of uterine neoplasia and died at age 42. The mother was reported to have had a similar cutaneous appearance to the proband.

On admission, the patient was in fair general condition, afebrile, with a blood pressure of 130/80 mmHg and conserved diuresis.

Examination of the integumentary system showed thickened, "cardboard-like" skin with muscle atrophy over limb joints and tendon retractions, consistent with post-GVHD localized scleroderma (Fig 1). Additionally, there was diffuse hyperpigmentation with multiple café-au-lait spots, cutaneous neurofibromas on the thorax, back, and abdomen, and axillary freckling (lentigines) (Fig 2). Neurological examination revealed peripheral neuropathy, with abolished reflexes in the upper limbs and weak patellar reflexes.

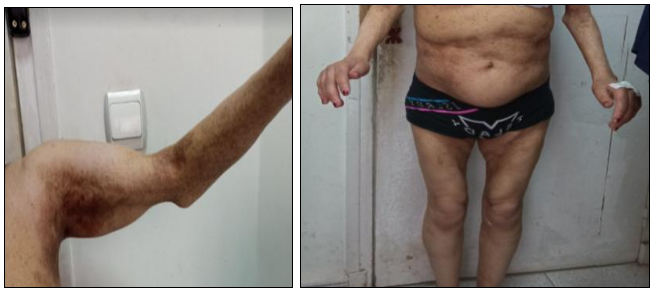

Image description: A clinical photograph of the patient's limb, showing thickened, tight, and shiny skin with tendon retractions and muscle atrophy, characteristic of localized scleroderma secondary to chronic GVHD.

Fig 1: Sclerodermiform Changes from Graft Versus Host Disease (GVHD)

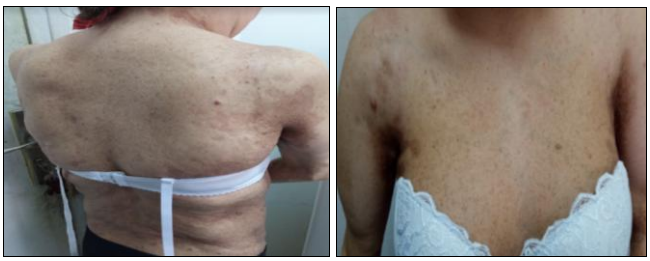

Image description: A clinical photograph showing the patient's torso, demonstrating multiple cutaneous neurofibromas (raised, fleshy nodules) and several café-au-lait macules (flat, hyperpigmented patches) scattered across the skin.

Fig 2: Cutaneous Stigmata of Neurofibromatosis Type 1.

The diagnostic work-up included laboratory tests and imaging studies. Blood tests showed hyperleukocytosis with neutrophilia, a C-reactive protein level of 28 mg/L, urea at 0.78 g/L, and serum creatinine elevated to 17 mg/L, which normalized after treatment. Urinalysis demonstrated proteinuria of 1200 mg/24h. The urinary sediment showed a few acanthocytes and leukocyturia, and the urine culture was positive for *Escherichia coli*. A hormonal work-up, including TSH, ACTH, cortisol, plasma renin activity, aldosterone concentration, and plasma and urinary metanephrines and catecholamines, was normal.

A comprehensive imaging and special investigation work-up was performed to explore the etiology of her hypertension and potential NF1-related complications. Echocardiography revealed mild septal hypertrophy, consistent with long-standing hypertension, and fundoscopic examination confirmed grade 2 hypertensive retinopathy. An abdominal CT scan ruled out obstructive uropathy, retroperitoneal neurofibromas, or other structural anomalies. Renal artery Doppler ultrasound, supplemented by cross-sectional angiography (CT/MR), showed no evidence of renal artery stenosis or vascular dysplasia. Further evaluations were conducted to assess for less common NF1-related contributors to renal impairment. There was no evidence of urinary tract compression, vesicoureteral reflux, or neurogenic bladder dysfunction. Slit-lamp examination, cerebral MRI, and skeletal surveys were unremarkable for other stigmata of NF1. Cystoscopy with bladder biopsy, performed to explore persistent urinary symptoms, revealed only non-specific inflammatory changes, with no tumor or neurofibromatous involvement identified.

The diagnosis of Neurofibromatosis Type 1 was formally established based on the fulfillment of the NIH diagnostic criteria, specifically the presence of three cardinal features: multiple café-au-lait macules, axillary freckling, and multiple cutaneous neurofibromas.

The patient was treated with double antibiotic therapy and intravenous rehydration for 10 days. Her renal function normalized, and she was discharged with a plan for multidisciplinary follow-up to manage her newly diagnosed NF1.

The patient's prolonged clinical course, marked by multiple referrals and a delayed diagnosis, is summarized in Table 1.

Table 1: Diagnostic timeline illustrating the 14-year delay in diagnosing Neurofibromatosis Type 1 (NF1)

Age (years)	Clinical Event or Finding	Medical Specialty Involved	Implication for NF1 Diagnosis
4	Onset of epilepsy	Pediatrics, Neurology	Potential early neurological manifestation of NF1
10	Diagnosis of severe hypertension	Pediatrics	Major red flag for secondary hypertension (e.g., NF1 vasculopathy)
13	Diagnosis and treatment of acute myeloid leukemia (with bone marrow transplant)	Pediatrics, Hematology, Oncology	NF1 is a known predisposition syndrome for JMML/AML
15	Development of chronic graft-versus-host disease with sclerodermiform skin lesions	Hematology, Oncology, Dermatology	Cutaneous GVHD likely overshadowed and masked NF1 skin signs
16	Secondary amenorrhea	Gynecology	Possible endocrinological complication or related to overall burden of disease
4-27	Presence of multiple café-au-lait spots, axillary freckling, and neurofibromas (present but unrecognized)	Not identified by any specialist	Classic diagnostic features of NF1, present but unrecognized
27	Hospitalization for acute renal failure / pyelonephritis leading to diagnosis of NF1	Nephrology	Unifying diagnosis established after a 14-year delay

The table highlights key clinical events, the involved medical specialties, and the relevance of each event to the eventual diagnosis of NF1. BMT: bone marrow transplant.

3. Discussion

This case illustrates a profound 14-year diagnostic delay of Neurofibromatosis Type 1 (NF1), finally uncovered in a nephrology unit. The patient had been followed by pediatricians, hematologists, oncologists, neurologists, and gynecologists, yet the unifying diagnosis was missed. Several factors contributed to this delay.

The patient's life-threatening conditions, including acute myeloid leukemia and chronic graft-versus-host disease (GVHD), rightfully dominated the clinical picture and overshadowed the cutaneous signs of NF1. The sclerodermiform changes resulting from GVHD may have further obscured or diverted attention from the neurofibromas and café-au-lait spots. Additionally, the patient transitioned between multiple specialists, each focusing on a specific organ system without a holistic, syndromic integration of her signs and symptoms across her lifespan. The admission for a common nephrological condition, pyelonephritis, provided an opportunity for a comprehensive physical examination that finally recognized the classic dermatological triad of NF1.

For nephrologists, NF1 is a diagnostically relevant entity because of its renal complications. Our patient had severe, early-onset hypertension, a major red flag for secondary causes. In NF1, hypertension can result from renovascular disease due to dysplastic vascular changes, which is the most common cause, as well as from pheochromocytoma or coarctation of the aorta [7, 11]. Renal artery stenosis is the most frequent vascular abnormality in NF1, occurring in approximately 4.7% of patients, and is associated with renal hypertension that is often refractory to medical therapy [8].

Although the renal artery Doppler was normal in our patient, the severity and early onset of her hypertension warrant consideration of these etiologies. A central nephrological paradox in this case is the presence of severe, early-onset hypertension requiring quadruple therapy in the context of a normal renal artery Doppler. While this result seemingly excludes main renal artery stenosis, the classic renovascular lesion in NF1, several explanations warrant consideration. First, NF1 vasculopathy can affect smaller, segmental, or intrarenal branches, which are notoriously difficult to visualize with standard Doppler ultrasonography and may require more sensitive imaging such as computed tomography angiography (CTA) or magnetic resonance angiography (MRA) for detection [8, 11]. Second, the hypertension may have been multifactorial. Long-term calcineurin inhibitor use for GVHD prophylaxis is a well-established cause of hypertension and could have been a significant contributor. Finally, the possibility of essential hypertension, though less likely given the early onset and severity, cannot be entirely ruled out. The normal Doppler, therefore, does not definitively exclude an NF1-related vascular component; it merely shifts the suspicion to a microvascular level or underscores the likelihood of a combined etiology. This highlights a critical learning point: in an NF1 patient with severe hypertension, a normal renal artery Doppler should not end the diagnostic inquiry but should prompt consideration of alternative vascular imaging and a review of iatrogenic contributors.

Pheochromocytoma is another important cause of hypertension in NF1. Germline mutations in the NF1 gene are found in approximately 7-22% of patients with pheochromocytomas and paragangliomas, particularly in those presenting at a younger age or with a family history of the disease [12, 13]. Although our patient's plasma and urinary metanephrines were normal, this association should be kept in mind when evaluating hypertensive NF1 patients.

Furthermore, the association between NF1 and myeloid malignancies, particularly juvenile myelomonocytic leukemia (JMML) and, less commonly, acute myeloid leukemia (AML), is well documented [14, 15]. The NF1 gene acts as a tumor suppressor, and its loss of function predisposes to certain cancers. The NF1 protein is a negative regulator of the RAS pathway, functioning as a RAS-GTPase activating protein; its inactivation provides an additional proliferative signal toward the development of leukemia [16]. Our patient's diagnosis of AML at age 13 is therefore a significant part of her NF1 phenotype and should have raised suspicion for an underlying neurocutaneous syndrome earlier in her clinical course.

Recent diagnostic criteria for NF1, revised in 2021, now include genetic testing as a confirmatory criterion, particularly useful in patients with atypical presentation or in children who have not yet developed sufficient characteristic clinical features [17] Approximately 97% of patients with NF1 can be diagnosed clinically by the age of 8 using the NIH criteria [18]. Our patient, however, had classic cutaneous signs present since childhood but remained undiagnosed until age 27, highlighting the continued importance of thorough physical examination even in adult patients with complex medical histories.

4. Limitations

This case report has several limitations. As a single observation, its findings are not generalisable. Genetic testing was not performed to confirm a pathogenic *NF1* variant; the diagnosis was made clinically based on NIH criteria. The patient's long and complex history, managed across multiple institutions, means that some historical data may be incomplete. Finally, while renovascular disease was thoroughly investigated with Doppler and cross-sectional angiography, the possibility of microvascular disease cannot be entirely excluded.

5. Conclusion

Neurofibromatosis Type 1 can present a significant diagnostic challenge in patients with complex, multi-system medical histories. The nephrologist can play a pivotal role in identifying this condition, especially when faced with early-onset or refractory hypertension. A meticulous physical examination seeking the classic cutaneous signs is a simple, cost-effective diagnostic tool. Recognising NF1 enables appropriate multidisciplinary follow-up to manage its potential renal and neoplastic complications.

6. Data Availability Statement

No new datasets were generated or analyzed during this study.

7. Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Neurofibromatosis Type 1. Syndrome, **C.S:** Review this manuscrit **A.B:** Supervision, head of the nephrology department, overall project administration.

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