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Juvenile xanthogranuloma in neurofibromatosis type 1. Prevalence and possible correlation with lymphoproliferative diseases: experience of a single center and review of the literature

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Abstract

Neurofibromatosis type 1 (NF1), is a rare genetic disorder that may involve almost every organ system in the body such as cutaneous, ophthalmologic and central and peripheral nervous system.

Cutaneous findings are usually the first sign of the disease. In this study, we investigate the real prevalence of xanthogranulomas juvenile (JXG) and possible correlation with lymphoproliferative diseases.

This is a retrospective study conducted on a population with NF1 followed by February 1983 to February 2022 at the "Sapienza" University of Rome, Italy.

We investigate the real prevalence of juvenile xanthogranuloma in NF1 and possible correlation with lymphoproliferative diseases. JXG was present in 39 cases (3.1%).

JXG is more frequent in NF1 than in the general population while the possible association with lymphoproliferative diseases in NF1 remains controversial. ***Clin Ter 2022; 173 (4):353-355 doi: 10.7417/CT.2022.2445***

Key words: *Juvenile xanthogranuloma, neurofibromatosis type 1, lymphoproliferative diseases*

Introduction

Neurofibromatosis type 1 (NF1), is a rare genetic disorder with an autosomal dominant transmission and an estimated incidence of 1:2500-3000 live birth. In about 50% of individuals, the disease is caused by a spontaneous mutation (1-3).

NF1 is determined by the inactivation of the tumor suppressor gene NF1(17q11.2) which encodes the protein neurofibromin, a 220 kDa guanosine triphosphate (GTP) ase-activating cytoplasmatic protein that is involved in cell growth regulation mechanisms by regulating the RAS protein. The consequence of the lack of neurofibromin results in an excess of the RAS-GTP active form, which promotes excessive cell growth, leading to deregulation and tumorigenesis (4-7).

NF 1 may involve almost every organ system in the body, with considerable inter-familial and intra-familial variation, there may be ophthalmologic, musculoskeletal, cardiovascular, gastrointestinal, autoimmune, endocrine, central and peripheral nervous system, and learning alterations (8-23). Patients with NF1 also have an increased susceptibility to develop tumors (24-27).

Cutaneous findings, which are readily apparent on visual inspection, are usually the first sign of the disease. Café au lait macules (CALMs), freckling on flexural areas and neurofibromas are particularly relevant because they comprise 3 of the 7 clinical diagnostic criteria of NF1. Other cutaneous manifestations are xanthogranuloma juvenile (JXG), nevus anemicus, Becker's nevus, spilus nevus, vitiligo, lipoma, psoriasis, melanoma and poliosis (28-39).

Methods

We investigate the real prevalence of JXGs in a population with NF1 followed by February 1983 to February 2022 at the "Sapienza" University of Rome, Italy. Patients were aged 1-87 years, included 625 females and 619 males.

NF1 patients in our clinic are seen usually every year by a dermatologist. Diagnosis of NF1 was made according to criteria from the NIH Consensus Conference. The diagnosis of JXG was made clinically.

JXG was defined as an asymptomatic yellow-brown papule or nodule with negative Darier sign and diffuse, homogeneous, orange-yellowish hue, surrounded by slight erythema at dermoscopy. Histopathologic confirmation was obtained in the 2 patients with a solitary JXG nodule.

Results

Five hundred and eighty (46.6%) had family history of NF1. CALMs were shown in 1201 (96.5%), axillary and

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inguinal freckling in 1099 (88.3%) while neurofibromas in 995 (80%). Juvenile xanthogranuloma (JXG) was present in 39 cases (3.1%).

Lesions were solitary in 77% of the cases. The number of JXGs varied greatly from patient to patient. The mean age at diagnosis of JXG was 4.1+-3.7 years. Although the JXGs occurred everywhere on the body surface except for the palmoplantar areas, a clear predilection for cephalic skin was observed (87%). In 10% of the cases, JXGs were present in more parts of the body. In one patient, a haematological disorder had been diagnosed (juvenile myelomonocytic leukemia).

Discussion and conclusions

Cutaneous manifestations are the most frequent alterations in NF1; they are usually the first sign of the disease and their presence is sufficient to make a diagnosis.

One cutaneous finding, which may be seen in young individuals with NF1, is JXG. JXG is a benign, self-involuting form of non-Langerhans cell histiocytosis, consisting of a singular, well-circumscribed, yellow-pink smooth papules (41). Histologically, JXGs are characterized by the presence of a dermal infiltrate of histocytes and other inflammatory cells such as eosinophils and characteristic Touton multinucleated giant cells.

JXG is uncommon in the general population while its prevalence in children with NF1 ranges from 0.7% to 37.5%. Ferrari proposed JXG as a minor diagnostic criterion for diagnosis of NF1 (42). Sbidian reported a prevalence of 3.9% in a series of 357 patients younger than 17 years (43). Marque reported a prevalence of 8.5% in 59 NF1 children (44). Fenot found JXGs in 15 of 40 NF1 children (35%) (45). Ferrari revealed JXGs in 30% of 20 NF1 children younger than 2 years; in contrast, JXGs were not observed in children older than 9 years or in adults.

The relationship between JXG and NF1 is unclear. The presence of a defect in the Ras pathway in JXG has not been investigated, although Emile found recurrent Ras mutations in Erdheim-Chester disease, which is also a non-Langherans cell histiocytosis (46). It might be that JXGs are associated with NF1 because of a loss of heterozygosity of the NF1 gene, as is the case for other skin manifestations of NF1.

Finally, although later denied (47), an association of JXG with juvenile myelomonocytic leukemia (JMML) had been hypothesized in patients with NF1. According to some authors, the risk of developing JMML is 20 to 30 times as high in patients with NF1 and multiple JXG lesions as in those without JXG lesions. These data have not been confirmed in some retrospective studies. Huson and Cambiaghi did not observe a significant difference in the prevalence of leukemia, in 40 children with and without JXG (48).

To our knowledge, a clonal relationship between JXGs and JMML has never been described. Neurofibromin interacts with the ras p21 protein and may regulate ras activity. Literature also suggests that activating ras mutations may result in increased T- or B-cell malignancies in animals. The association between haematologic malignancies and germ-line mutations of NF1 gene has been established in the pediatric setting. Children with NF1 have a 500-fold increased risk of developing a rare form of leukemia, known as JMML (30,49,50).

The association between NF1, JXG and JMML might be coincidental because both JXG and malignancy are associated with NF-1.

In, our case, JXGs were present in 3.1% of all NF1 patients examined, while JXGs and juvenile myelomonocytic leukemia were present at the same time in only one case.

The coexistence of JXG and malignancy because they are associated with NF-1. Patients with NF-1 should be monitored for malignancy regardless of the presence or absence of JXG.

References

1. Bottillo I, Torrente I, Lanari V, et al. Germline mosaicism in neurofibromatosis type 1 due to a paternally derived multiexon deletion. Am J Med Genet A. 2010;,152:1467-73
2. Pinna V, Daniele P, Calcagni G, et al. Prevalence, Type, and Molecular Spectrum of NF1 Mutations in Patients with Neurofibromatosis Type 1 and Congenital Heart Disease. Genes (Basel). 2019; 10(9)
3. Wallis D, Li K, Lui H et al. Neurofibromin (NF1) genetic variant structure-function analyses using a full-length mouse cDNA. Hum Mutat. 2018; 39:816-21
4. Pinna V, Lanari V, Daniele P, et al. p.Arg1809Cys substitution in neurofibromin is associated with a distinctive NF1 phenotype without neurofibromas. Eur J Hum Genet. 2015; 23:1068-71
5. Koczkowska M, Callens T, Chen Y, et al. Clinical spectrum of individuals with pathogenic NF1 missense variants affecting p.Met1149, p.Arg1276, and p.Lys1423: genotype-phenotype study in neurofibromatosis type 1. Hum Mutat. 2020; 41:299-315
6. Rauen KA, Huson SM, Burkitt-Wright E, et al. Recent developments in neurofibromatoses and RASopathies: management, diagnosis and current and future therapeutic avenues. Am J Med Genet. 2014; 12:1-10
7. De Luca A, Bottillo I, Dasdia MC, et al. Deletions of NF1 gene and exons detected by multiplex ligation-dependent probe amplification. J Med Genet. 2007; 44:800-8
8. Gutmann DH, Ferner RE, Listernick RH, et al. Neurofibromatosis type 1. Nat Rev Dis Primers. 2017; 3:17004
9. Miraglia E, Iacovino C, Cantisani C, et al. An unusual manifestation in a patient with Neurofibromatosis type 1. G Ital Dermatol Venereol. 2016;151:129-30
10. Moramarco A, Giustini S, Nofroni I, et al. Near-infrared imaging: an in vivo, non-invasive diagnostic tool in neurofibromatosis type 1. Graefes Arch Clin Exp Ophthalmol. 2018; 256:307-11
11. Moramarco A, Giustini S, Miraglia E, et al. SD-OCT in NIR modality to diagnose retinal microvascular abnormalities in neurofibromatosis type 1. Graefes Arch Clin Exp Ophthalmol. 2018; 256:1789-90
12. Moramarco A, Lambiase A, Mallone F, et al. A characteristic type of retinal microvascular abnormalities in a patient with Neurofibromatosis type 1. Clin Ter. 2019;170:e4-e9
13. Nebbioso M, Moramarco A, Lambiase A, et al. Neurofibromatosis Type 1: Ocular Electrophysiological and Perimetric Anomalies. Eye Brain. 2020;12:119-27
14. Moramarco A, Miraglia E, Mallone F, et al. Retinal microvascular abnormalities in neurofibromatosis type 1. Br J

Ophthalmol. 2019; 103:1590-4
15. Nebbioso M, Moramarco A, Lambiase A, et al. Neurofibromatosis Type 1: Ocular Electrophysiological and Perimetric Anomalies. Eye Brain. 2020 Oct 21;12:119-27
16. Moramarco A, Sacchetti M, Franzone F, et al. Ocular surface involvement in patients with neurofibromatosis type 1 syndrome. Graefes Arch Clin Exp Ophthalmol. 2020 Aug; 258(8):1757-62
17. Friedman JM, Arbiser J, Epstein JA, et al. Cardiovascular disease in neurofibromatosis 1: report of the NF1 Cardiovascular Task Force. Genet Med. 2002; 4:105-11
18. Miraglia E, Calvieri S, Giustini S. Neurofibromatosis type 1 and lichen sclerosus: an uncommon association. G Ital Dermatol Venereol. 2017; 152:83-4
19. Anderson JL, Gutmann DH. Neurofibromatosis type 1. Handb Clin Neurol. 2015; 132:75-86
20. Lopez T, Miraglia E, Calvieri S, et al. Two sisters with neurofibromatosis type 1 and celiac disease. G Ital Dermatol Venereol. 2018; 153:444-6
21. Basile U, Cavallaro G, Polistena A, et al. Gastrointestinal and retroperitoneal manifestations of type 1 neurofibromatosis. J Gastrointest Surg. 2010; 14:186-94
22. Miraglia E, Fabbrini G, Di Biasi C, et al. Chiari type 1 malformation in Neurofibromatosis type 1: experience of a center and review of the literature. Clin Ter. 2016; 167:e6-10
23. Garcia-Penas JJ. Learning disorders in neurofibromatosis type 1. Rev Neurol. 2017; 64:59-63
24. Miraglia E, Pecorella I, Persechino F, et al. A rare association between neurofibromatosis type 1 and vulvar sarcoma. G Ital Dermatol Venereol. 2014; 149:374-6
25. Zinnamosca L, Petramala L, Cotesta D, et al. Neurofibromatosis type 1 (NF1) and pheochromocytoma: prevalence, clinical and cardiovascular aspects. Arch Dermatol Res. 2011; 303:317-25
26. Miraglia E, Lopez T, Calvieri S et al. Giant plexiform neurofibroma in neurofibromatosis type 1. G Ital Dermatol Venereol. 2018;153:740-1
27. Peltonen S, Kallionpää RA, Rantanen M, et al. Pediatric malignancies in neurofibromatosis type 1: A population-based cohort study. Int J Cancer. 2019 Dec 1; 145(11):2926-2932
28. Miraglia E, Moliterni E, Iacovino C, et al. Cutaneous manifestations in neurofibromatosis type 1. Clin Ter. 2020 Sep-Oct;171(5):e371-e377
29. Ozarslan B, Russo T, Argenziano G, et al. Cutaneous Findings in Neurofibromatosis Type 1. Cancers (Basel). 2021 Jan 26; 13(3):463
30. Miraglia E, Fino P, Calvieri S, et al. Juvenile myelomonocytic leukemia in a patient with neurofibromatosis type 1 and xanthogranulomas. G Ital Dermatol Venereol. 2019; 154:717-8
31. Ben-Shachar S, Dubov T, Toledano-Alhadef H, et al. Predicting neurofibromatosis type 1 risk among children with isolated café-au-lait macules. J Am Acad Dermatol. 2017; 76:1077-83.e3
32. Miraglia E, Iacovino C, Calvieri S, et al. Nevus anemicus in neurofibromatosis type 1. G Ital Dermatol Venereol. 2021 Dec;156(Suppl. 1 to No. 6):103-104
33. Miraglia E, Iacovino C, Calvieri S, et al. Becker's nevus in neurofibromatosis type 1: a single center experience in Italy. G Ital Dermatol Venereol. 2017; 152:545-7
34. Fadda MT, Giustini S, Verdino G, et al. Role of maxillofacial surgery in patients with neurofibromatosis type I. J Craniofac Surg. 2007 May;18(3):489-96
35. Cavallaro G, Basile U, Polistena A, et al. Surgical management of abdominal manifestations of type 1 neurofibromatosis: experience of a single center Am Surg. 2010;76:389-96
36. Miraglia E, Fino P, Lopez T, et al. Multiple lipomas in a patient with Neurofibromatosis Type 1.G Ital Dermatol Venereol. 2019; 154:734-5
37. Miraglia E, Cantoresi F, Calvieri S, et al. Coexistence of neurofibromatosis type 1 and psoriasis: more than a simple association. G Ital Dermatol Venereol. 2016; 151:447-8
38. Miraglia E, Calvieri S, Giustini S. Is there an association between neurofibromatosis type I and vitiligo? G Ital Dermatol Venereol. 2017; 152:388-90
39. Miraglia E, Lopez T, Iacovino C, et al. Melanoma in neurofibromatosis type 1: an Italian single center experience. G Ital Dermatol Venereol. 2019; 154:89-91
40. Miraglia E, Calvieri S, Giustini S. Pruritus in neurofibromatosis type 1. G Ital Dermatol Venereol. 2018; 153:120-2
41. So N, Liu R, Hogeling M. Juvenile xanthogranulomas: Examining single, multiple, and extracutaneous presentations. Pediatr Dermatol. 2020; 37(4):637-644
42. Ferrari F, Masurel A, Olivier-Faivre L, et al. Juvenile xanthogranuloma and nevus anemicus in the diagnosis of neurofibromatosis type 1. JAMA Dermatol 2014; 150:42-6
43. Sbidian E, Hadj-Rabia S, Riccardi VM, et al. Clinical characteristics predicting internal neurofibromas in 357 children with neurofibromatosis-1: results from a cross-selectional study. Orphanet J Rare Dis. 2012 Sep 3; 7:62
44. Marque M, Roubertie A, Jaussent A, et al. Nevus anemicus in neurofibromatosis type 1: a potential new diagnostic criterion. J Am Acad Dermatol 2013; 69:768-75
45. Fenot M, Stalder JF, Barbarot SJ. Juvenile xanthogranulomas are highly prevalent but transient in young children with neurofibromatosis type 1. Am Acad Dermatol. 2014 Aug; 71(2):389-90
46. Emile JF, Diamond EL, Helias-Rodzewicz Z, et al. Recurrent RAS and PIK3CA mutations in Erdheim-Chester disease. Blood 2014; 124:3016-9
47. Liy-Wong C, Mohammed J, Carleton A, et al. The relationship between neurofibromatosis type 1, juvenile xanthogranuloma, and malignancy: A retrospective case-control study. J Am Acad Dermatol. 2017; 76:1084–1087
48. Cambiaghi S, Restano L, Caputo R. Juvenile xanthogranuloma associated with neurofibromatosis 1: 14 patients without evidence of hematologic malignancies. Pediatr Dermatol. 2004; 21:97-101
49. Hernández-Martín A, Duat-Rodríguez A. An Update on Neurofibromatosis Type 1: Not Just Café-au-Lait Spots and Freckling. Part II. Other Skin Manifestations Characteristic of NF1. NF1 and Cancer. Actas Dermosifiliogr. 2016; 107:465-73
50. Roberti V, Miraglia E, Laghi A, et al. Tumors in patients with neurofibromatosis type 1: a single- center retrospective study. Clin Ter. 2022; 173(2):135-140