G Chir Vol. 28 - n. 5 - pp. 199-202
Maggio 2007

casistica clinica

Adrenal pheochromocytoma and jejunal neurofibroma in type 1 neurofibromatosis: report of a case

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SUMMARY: Adrenal pheochromocytoma and jejunal neurofibroma in type 1 neurofibromatosis: report of a case.

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Introduction - *Neurofibromatosis type 1 (NF1), known as von Recklinghausen's disease, is characterized by presence of café au lait spots, and neurofibromas in the skin or along the course of peripheral nerves. Diagnosis, despite extreme clinical variability, is defined by established diagnostic criteria. Clinical status is frequently complicated by systemic disorders and neoplasias.*

Case report - *A case of a patient affected by NF1, with hypertension due to adrenal pheochromocytoma and with jejunal neurofibroma, is reported.*

Discussion and conclusions - *Variability in clinical presentation of NF1 with possible manifestation of severe systemic benign and malignant diseases requires strict follow-up and specific screening of extracutaneous lesions.*

RIASSUNTO: Feocrocitoma e neurofibroma digiunale in paziente affetto da neurofibromatosi tipo 1: case report.

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Introduzione - *La neurofibromatosi tipo 1 (NF1), conosciuta come malattia di von Recklinghausen, è caratterizzata dalla presenza di macchie caffelatte e neurofibromi cutanei o lungo il decorso dei nervi periferici. La diagnosi è codificata da precisi criteri. Il quadro clinico è spesso complicato da neoplasie o disordini sistemici.*

Case report - *Gli Autori presentano il caso di un paziente affetto da NF1 con ipertensione secondaria alla presenza di feocromocitoma surrenalico e con neurofibroma digiunale.*

Discussione e conclusioni - *La variabilità nella presentazione clinica della NF1, con possibili manifestazioni sistemiche e neoplasie, richiede uno stretto follow-up e screening specifici per eventuali malattie extra-cutanee.*

KEY WORDS: Jejunal neurofibroma - Pheocromocitoma - Type 1 neurofibromatosis.
Neurofibroma digiunale - Feocromocitoma - Neurofibromatosi tipo 1.

Introduction

Neurofibromatosis type 1 (NF1), known as von Recklinghausen's disease, is the most common familial disease, with a prevalence of 1/3000, characterized by the presence of peripheral nerve tumors.

NF1 gene, located in 17q11.2, produces a protein named neurofibromina, whose action consists in disfunction of *p21-ras* oncogene (1-5).

Variety in clinical presentation represents one of the most important clinical issues in NF1, partially solved by classification of diagnostic criteria defined in 1987 by the American National Institute of Health (NHI) Consensus Development Conference (Tab. 1) (6).

Skin neurofibromas, rare in childhood, increase in number by the age, whereas *cafè au lait* spots, often the first clinical manifestation, decrease after fifties. In patients affected by NF1 clinical status deterioration is most frequently associated to skeletal disease, neoplasias, neurological disorders and plexiform neurofibromas. In addition to cutaneous neurofibromas, patients with NF1 may develope benign and even malignant neoplasms, including intestinal tumors, malignant gliomas, juvenile chronic myeloid leukemia and tumors of neuroectodermal origin, such as pheochromocytoma (7-9).

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TABLE 1 - DIAGNOSTIC CRITERIA NATIONAL INSTITUTE OF HEALTH CONSENSUS DEVELOPMENT CONFERENCE 1987. NEUROFIBROMATOSIS: CONFERENCE STATEMENT (ref. 6).

1	Six or more *cafè au lait* spots (≥ 5 mm in children, ≥ 15 mm in adults)
2	Two or more neurofibromas of different type or a plexiform neurofibroma
3	Axillary or inguinal lentigines
4	Glioma of the nervus opticus
5	One or more Lisch's nodules
6	Bone disorders
7	Familiarity for NF1 diagnosed as above

Patients followed up for NF1 in the Department of Cutaneous Diseases and Plastic Surgery, University of Rome "La Sapienza", undergo regular screening for early diagnosis of general disorders. Annual follow up is carried out by clinical examination, whereas ophthalmologic and psychiatric evaluation is provided for younger patients. Specific imaging (CT-scan, MR imaging) and consultation are performed in case of suspicion of systemic involvement.

The Authors report a case of association of NF1, left adrenal pheochromocytoma and jejunal neurofibroma causing sub-clinical intestinal stenosis.

Case report

A 42-years-old male patient has been followed up with diagnosis of NF1 with typical cutaneous neurofibromas (Fig. 1) since 38 in the Department of Cutaneous Diseases and Plastic Surgery of the University of Rome "La Sapienza".

During the last clinical examination the patient, due to symptomatic tachycardia, underwent ECG which showed sinusal tachycardia (105 heart rate/min), and elevated blood pressure in supine position (145/90 mmHg). Therefore the patient was referred to the Day Hospital of Internal Medicine and Hypertension of the Department of Clinical Sciences. On admission, the blood pressure was 140/90 mmHg and 125/75 mmHg in upright position. Ambulatory monitoring of blood pressure (AMBP) revealed paroxistic hypertension (180/115 mmHg) without night-time drop < 10% (not-dipper). Dosage of urinary vanillyl mandelic acid (12 mg/24h, normal range 1-11), plasma chromogranin-A (152 µg/ml, normal value < 90) and of urinary methanephrines (480 mg/24h, normal range 20-345) indicated high suspicion of pheochromocytoma. On the other side the patient showed normal values of calcium and phosphorus, of the hypotalamic-hypophysis-adrenal hormones (ACTH 17.6 pg/ml, cortisol 18 mg/ml, aldosterone 44.3 pg/ml, plasmatic renin activity 0.98 ng/ml/h) and normal thyroid function.

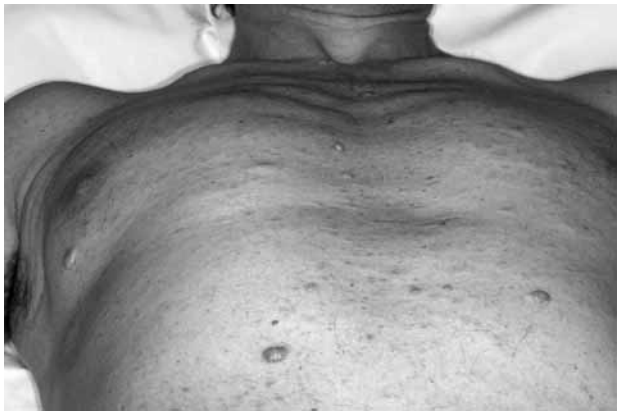

Fig. 1 - Cutaneous neurofibromas.

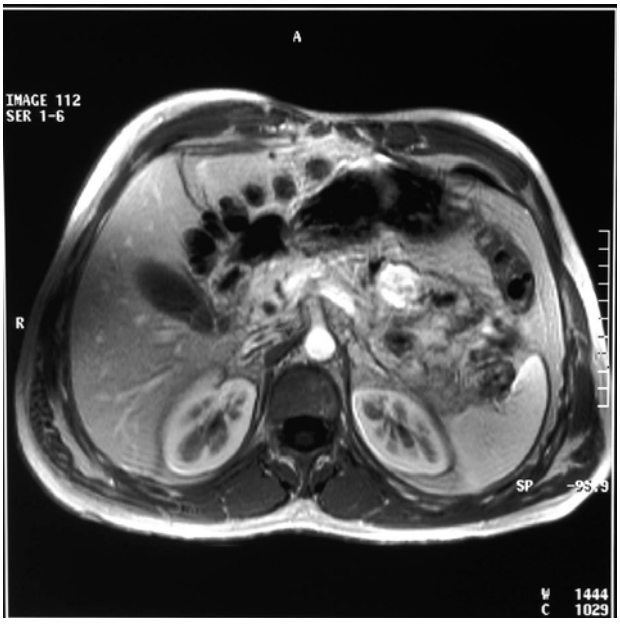

Fig. 2 - MR demonstrates enlargement of left adrenal gland.

Based on the considerations above the patient underwent abdominal magnetic resonance (Fig. 2), which demonstrated a 15x12 mm nodule, located at the level of the left adrenal gland. This was confirmed by MIBG-scan (Fig. 3).

After adequate pre-treatment with α- and β-blockers (doxazosin 4 mg/day and propanolol 40 mg/day) the patient underwent left adrenalectomy through median laparotomy. During surgical exploration a spherical 3.5 cm large neoplasm, involving the first portion of jejunum (Fig. 4), which appeared compressed, was found. Since tight junction to the bowel, an *en-bloc* short jejunal resection was performed with hand-sewn end-to-end anastomosis.

Pathologic examination showed respectively adrenal pheochromocytoma and jejunal neurofibroma.

The immediate postoperative course ran regularly and the patient was discharged from the hospital on the 10th day. After four months the patient is doing well, with normal blood pressure and hearth rate, normal blood pressure rythm, as well as dosage of urinary vanillyl mandelic acid (6.5 mg/24h), plasma chromogranin-A (56 µg/ml) and of urinary methanephrines (256 mg/24h).

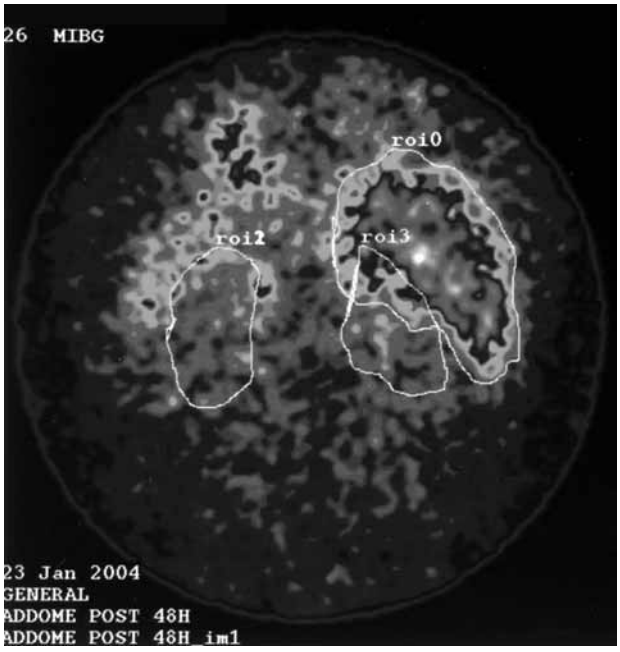

Fig. 3 - MIBG scintigraphy reveals ipercaptation by left adrenal medulla.

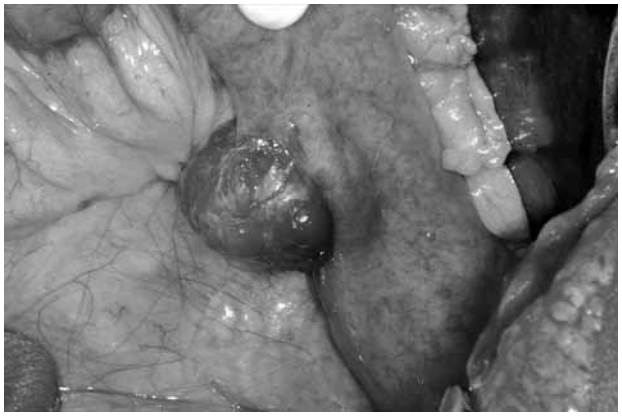

Fig. 4 - Intraoperative view of the jejunal neurofibroma.

Discussion

NF1 is a common autosomal dominant disorder, characterised by the presence of *cafè au lait* spots, peripheral neurofibromas, Lisch's nodules and freckling.

Diagnosis of NF1, although difficult for the extreme variability in clinical presentation, is nowadays defined by presence of at least two of the diagnostic criteria established by the National Institute of Health Consensus Development Conference in 1987 (6). As well it has been suggested that the clinical behaviour of NF1 may be graded in four levels, from minimal to severe compromised clinical status. Indeed from simple localized cutaneous or nerve lesions, NF1 may present orthopaedic or neurological disorders up to neoplastic diseases.

Since increased frequency of malignancy, NF1 is burdened by increased mortality compared to general population. Chronic myeloid leukaemia, neurofibrosarcoma, Vater's ampulla carcinoma, non-Hodgkin lymphoma, lymphoblastic leukaemia, and rabdomiosarcoma are the most frequent neoplasias described associated to NF1 (7, 15). Furthermore other rare tumors as pheochromocytoma have been found in patients with NF1 (7-14).

In 1910 Suzuki first recognized the association of pheochromocytoma to von Recklinghausen's disease (15), which has been reported by many authors in isolated cases. The estimated prevalence of pheochromocytoma in NF1 is between 0.1% and 5.7%, but this tumor has been found at autopsy in 3.3-13% of NF1 patients (16) The mean age at diagnosis of pheochromocytoma in these patients was 42 years, with bilateral adrenal involvement in 9.6% and ectopic pheochromocytoma presentation in 6.1% of cases. Clinical symptomps attributable to pheochromocytoma were present in 61% of patients (9). The presented case confirms the importance of this clinical manifestation in systemic advanced NF1.

Since there is no reliable genetic test to define the possible phenotypic expression of different genomic patterns, it is evident the necessity of a strict follow-up in NF1 patients in order to identify precocious clinical signs of extra-cutaneous diseases.

Furthermore several reports describe the presence of intestinal neurofibromas in advanced neurofibromatosis. Visceral tumours arising in the neural plexus of the intestinal wall may cause ulceration, bleeding, obstruction, perforation and palpable abdominal mass (17-20). Involvement of other visceral structures (vessels, urinary bladder) has been also described (21, 22).

These conditions, often symptomatic or sometimes found intraoperatively for other disorders, may require surgery to be solved.

Conclusions

The presented clinical case is a typical example o possible multiple systemic involvement of advanced NF1, in which cutaneous disease was associated to adrenal medulla neoplasia and intestinal disease.

In conclusion variability in clinical presentation of NF1, with possible manifestation of severe systemic benign and malignant diseases, requires strict follow-up and programs of specific screening in order to obtain precocious diagnosis of extra-cutaneous lesions.

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