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# Association of Urticaria pigmentosa with Café-au-Lait Spots, Neurofibromas and Neurofibroma-Like Neoplasms: A Mere Coincidence?

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**Key Words**
Mast cell · Urticaria pigmentosa · Neurofibroma · Oncogenesis

**Abstract**
***Background:*** Urticaria pigmentosa (UP) is characterized by dense aggregates of mast cells in the dermis. There is consistent evidence from the literature that mast cells may play a pathogenetic role in the development of neurofibromas and other tumors. ***Objective:*** To study the concomitant appearance of UP with neurofibromas and neurofibroma-like neoplasms. ***Methods:*** We analyzed 31,752 records of patients examined at the Department of Dermatology in the year 2000, looking for UP and associated neurofibromas and neurofibroma-like neoplasms in persons younger than 18 years. ***Results:*** We identified a total of 27 patients suffering from UP, with 16 persons younger than 18 years. One 12-year-old Caucasian boy demonstrated multiple cutaneous mastocytomas consistent with the diagnosis of UP. On his trunk, four café-au-lait spots were found. A cutaneous neurofibroma was confirmed by skin biopsy. Magnetic resonance imaging detected multiple neoplasms located at the nerve roots of the spine, resembling plexiform neurofibromas. ***Conclusions:*** There may be a concomitant appearance of UP and neoplasms, with mast cells possibly playing a causative role. The existence of neoplasms, including neurofibromas and neurofibroma-like lesions should be considered when examining UP cases.



## Introduction

Mastocytosis compromises several clinical disorders characterized by overproliferation and accumulation of tissue mast cells. The clinical signs vary and depend on local amassment of mast cells in different organs and the effects of their mediators [1]. Urticaria pigmentosa (UP), seen in about two thirds of patients with cutaneous mastocytosis, is the most common form of childhood mastocytosis [2].

Clinically, the disease is characterized by multiple reddish brown macular, papular, or nodular lesions, that tend to be oval or round. Scratching active lesions of UP will result in urtication (positive Darier's sign).

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Mast cells are widely distributed in nearly every organ, often close to blood and lymphatic vessels, peripheral nerves, and epithelial surfaces, and they have been found in a variety of benign and malignant tumors in humans, except gliomas [1, 3].

According to considerations by Binnazi and Landi [4] and Riccardi [5, 6], mast cells may play a pathogenetic role in the development of neurofibromas and other tumors. To elucidate this association, we screened UP children for the presence of neurofibromas and neurofibroma-like lesions.

## Methods

We analyzed all available files of patients diagnosed with UP by clinical examination (macroscopic aspect; positive Darier's sign) with and without biopsy of lesional skin and younger than 18 years for associated neurofibromas and neurofibroma-like lesions.

All patients had been examined at the Department of Dermatology and Allergy Biederstein, Technical University of Munich, Germany, between 1 January 2000 and 31 December 2000.

## Results

A total of 31,752 outpatient files were screened. Twenty-seven patients (19 female, 8 male) had been diagnosed with UP (overall 1-year prevalence: 0.085%), including 16 patients (11 female, 5 male) younger than 18 years of age. UP and signs of neoplasm were confirmed in 1 childhood case: a 12-year-old male Caucasian patient showed more than 40 round to oval, reddish brown macules and papules (fig. 1, 2) with positive Darier's sign, distributed diffusely on trunk and extremities.

Skin biopsies with formalin-fixed, paraffin-embedded sections demonstrated: (1) increased numbers of mast cells throughout the full thickness of the dermis, without pleomorphism and mitoses (stains used: HE and toluidine blue); corresponding to the clinical diagnosis of mastocytoma; (2) a well-delineated but unencapsulated spindle cell tumor with small nerve fibers and mast cells without mitoses classified as neurofibroma [fig. 3a, b; stains used: HE; S-100 protein (positive); neuron-specific enolase (mild positive)]. The very first mastocytomas had appeared at the age of 5 years. According to the parents, developmental milestones were reached without delay. In the past, intermittent episodes of diarrhea had been encountered. No family member was reported to suffer from mastocytosis and other cutaneous disorders.

Further clinical examination demonstrated 4 light-brown hyperpigmented, sharply demarcated macules measuring 0.5–4 cm in diameter on the patient's trunk, classified as café-au-lait spots (fig. 2). Axillary freckling and Lisch nodules were absent. In the thoracic region, a funnel chest (fig. 1) was found whereas on his left buttock a blue-black well-circumscribed macule, measuring 8 × 6 cm, classified macroscopically as Mongolian spot, was detected. Weight, height and head circumference measured at the 50th centile.

Blood analysis (including basal serum tryptase concentration) and urine (including 24-hour collection of histamine) were within normal range.

Magnetic resonance (MR) imaging of head, neck, thorax and abdomen revealed space-occupying lesions in every nerve root emerging from the spine, resembling radiologically plexiform neurofibromas (fig. 4a, b). Cerebellum, dentate nucleus, hippocampus, brain stem and quadrigeminal plate depicted several high signal lesions on T2-weighted MR images. Below the occipital skin surface, subtle lesions resembling small neurofibromas were identified. Additional cardiovascular, pulmonal, gastrointestinal, endocrinological, ophthalmological, neurological as well as psychometrical examinations had been uneventful. Biopsies of paraspinal neurofibroma-like lesions and bone-marrow as well as gene analysis were not permitted by the parents. According to the neurofibromatosis categories presented by Riccardi [5], the patient was diagnosed to suffer most probably from a *forme fruste* of neurofibromatosis (type 1?) and UP.

## Discussion

We describe a case of cutaneous mastocytosis associated with café-au-lait spots, cutaneous neurofibroma and paraspinal plexiform neurofibroma-like lesions in a 12-year-old white boy.

Mast cells derive from pluripotent bone-marrow progenitor cells that express CD 34 antigen and undergo proliferation and maturation in specific tissues [7]. Mastocytosis refers to a group of clinical disorders that are histologically characterized by mast cell hyperplasia. Although an elaborated consensus proposal has been generated recently [8], a modified version [1] of a 1991 proposal by Metcalfe [9] for the classification of mastocytosis is still in clinical use (table 1).

The reason for proliferation and accumulation of mast cells in mastocytosis is not completely understood. Longley et al. [10] demonstrated increased concentrations of

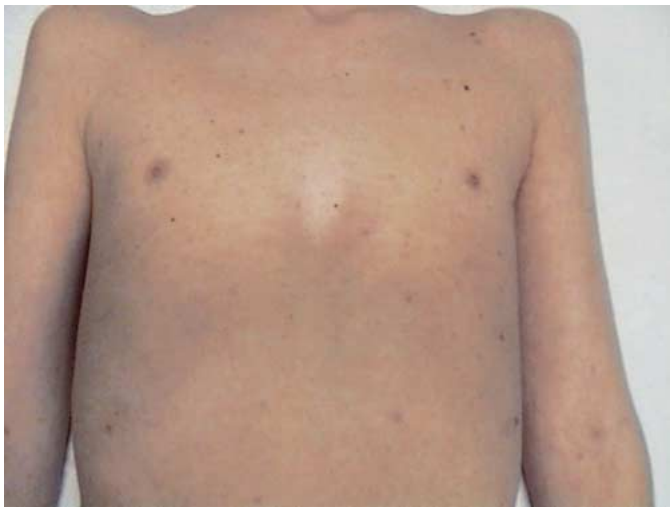

**Fig. 1.** Frontal view of chest, abdomen and upper extremities with multiple mastocytomas in UP patient. Note also pectus excavatum.

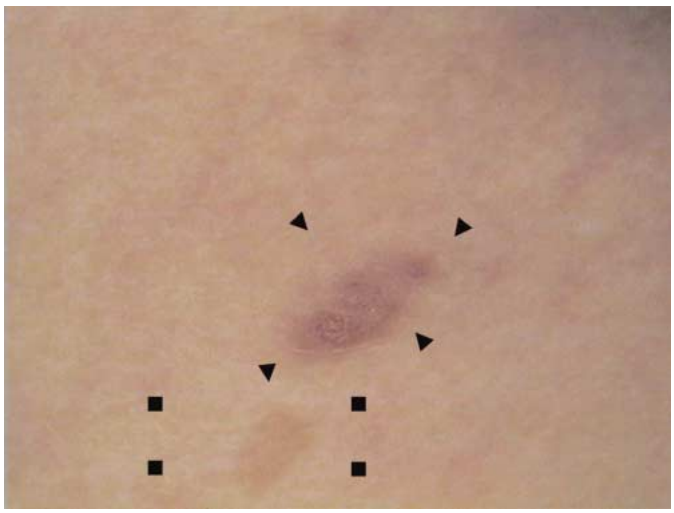

**Fig. 2.** Truncal mastocytoma (▼) and café-au-lait spot (■) in UP patient.

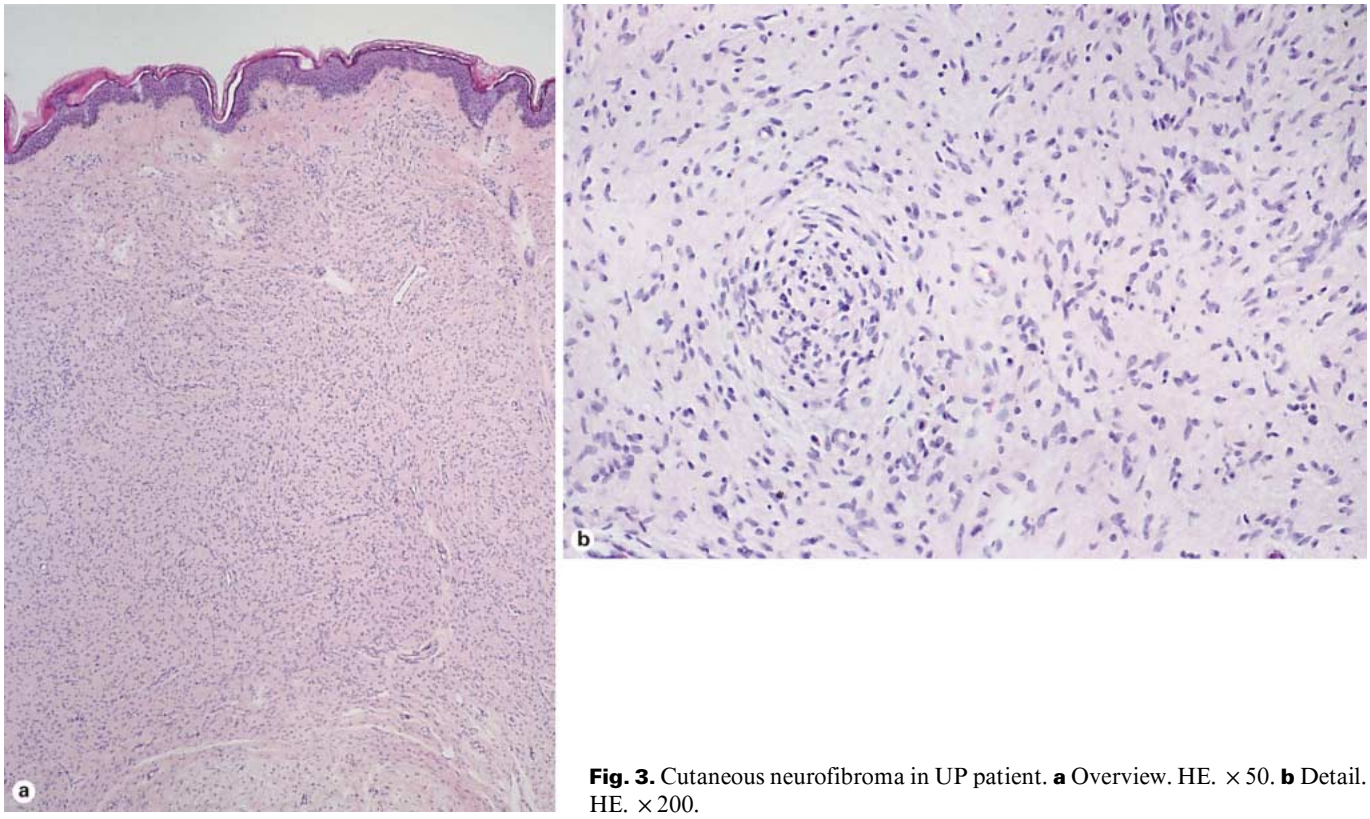


**Fig. 3.** Cutaneous neurofibroma in UP patient. **a** Overview. HE. × 50. **b** Detail. HE. × 200.

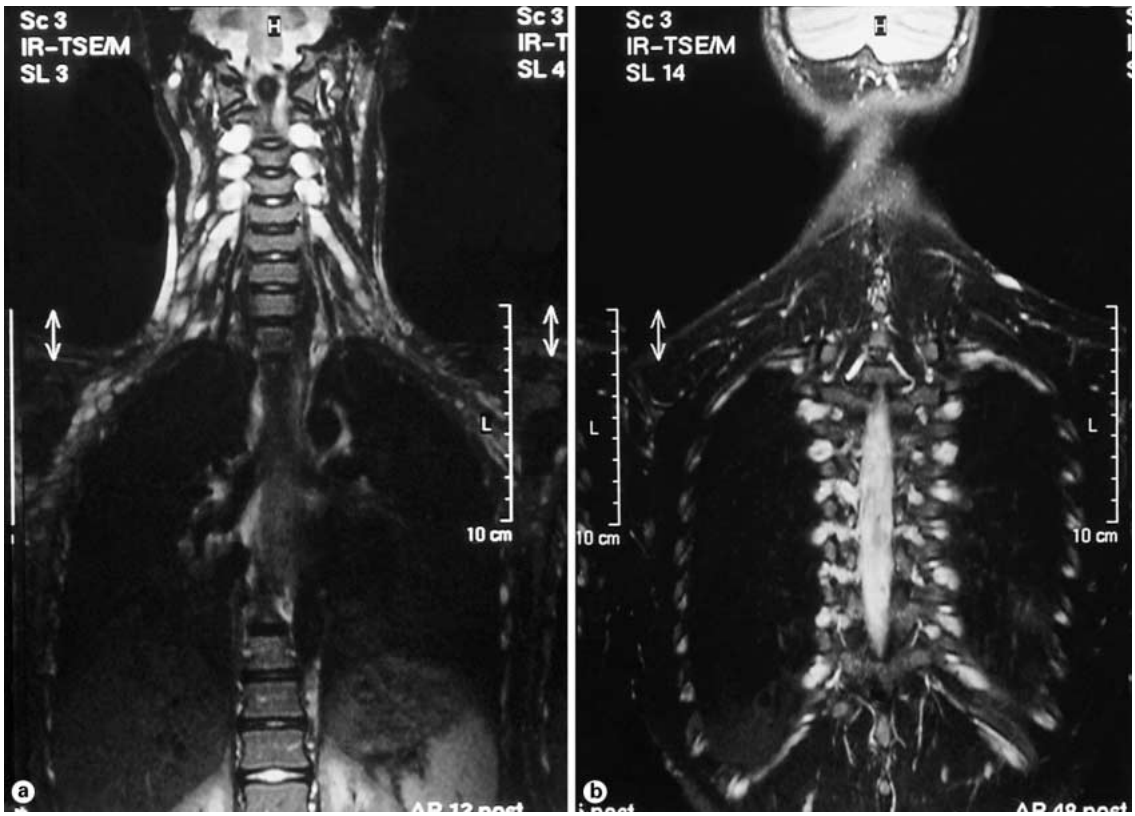


**Fig. 4.** MR images of plexiform paravertebral neurofibroma-like neoplasms of the cervical (**a**) and thoracic (**b**) region.

**Table 1.** Classification of mastocytosis

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|---|
| Cutaneous mastocytosis |
| Urticaria pigmentosa |
| Solitary mastocytoma |
| Diffuse cutaneous mastocytosis |
| Teleangiectasia macularis eruptiva perstans |
| Systemic mastocytosis, with or without skin involvement |
| Mast cell infiltration of at least one internal organ |
| Mastocytosis in association with hematologic disorder, with or without skin involvement |
| Leukemia, lymphoma, myelodysplastic, myeloproliferative disorders and others |
| Lymphadenopathic mastocytosis with eosinophilia, with or without skin involvement |
| Mast cell leukemia |

Classification according to Golkar et al. [1] and Metcalfe [9].

the soluble form of mast cell growth factor in cutaneous mastocytosis lesions. Furthermore, mast cell-expressed *c-kit* receptors, which interact with mast cell growth factor in the development of mast cells, may show mutations or other abnormalities resulting in a disordered mast cell proliferation [1, 11].

Mast cells may be activated by IgE-mediated and IgE-independent mechanisms, resulting in a release of various mediators that are stored in secretory granules, as well as synthesis of membrane-derived lipid metabolites and inflammatory cytokines [1]. Mast cell-derived mediators may act on a systemic level, causing flushing, hypotension, headache, or neuropsychiatric dysfunction, and on a microenvironmental level, responsible for localized pruritus, development of fibrosis in bone marrow or liver, or mucous membrane edemas in the respiratory and digestive system [12].

Although we found a female-male ratio of 2:1, cutaneous mastocytosis has been reported to occur equally in both sexes [13]. Our detected frequency of 1 case in every 1,176 outpatient visits agrees well with the reported

occurrence estimated as 1 case in every 1,000–8,000 dermatology outpatient consultations [1].

Nevertheless, our observed frequency may represent an underestimation since we did not perform lesional biopsy in every examined patient, thereby missing cases lacking clinically obvious skin lesions [14].

UP is the most common cutaneous manifestation of mastocytosis in children and adults with a hitherto unknown prevalence [1, 13]. With the limitations mentioned above, we found a general 1-year prevalence of 0.085% in a dermatologic outpatient setting. Historically, UP was first described in 1869 by Nettleship and Tay [15], whereas extracutaneous involvement of organs was demonstrated in 1933 [16]. The prognosis of UP obviously depends on the clinical presentation and age of onset. Patients younger than age 10 almost always encounter spontaneous full or partial resolution of lesions by adolescence or adulthood [17]. Although association of UP with systemic mast cell infiltrates has been reported in up to 5% of patients with onset of UP before age 10 (as compared with 10% or more in older children), it was found that these children had diffuse cutaneous or erythrodermic forms of mastocytosis rather than true UP [2]. In respect to our patient, a systemic mastocytosis cannot be excluded with certainty since invasive procedures (e.g. bone marrow biopsy) had been refused by the parents.

Whereas Greggio [18] described large numbers of mast cells in neurofibromas as early as 1911, Binnazi and Landi [4], 40 years ago, were probably the first to consider a contribution of mast cell secretions to the pathogenesis of neurofibroma growth. In 1984, Mérot et al. [19] reported the case of a 62-year-old Swiss woman suffering from asymptomatic systemic mastocytosis with bone marrow involvement, neurofibromas and café-au-lait spots [19].

Among released mast cell mediators, histamine and heparin have been characterized as potent mitogens and angiogenetic factors that may directly contribute to neurofibroma growth [20, 21]. In 1995, Reed et al. [22] demonstrated the expression of basic fibroblast growth factor, a potent chemotactic, mitogenic and angiogenic factor in vitro that binds to intracellular heparin of mast cells in benign cutaneous mastocytomas and solitary neurofibromas of humans. Reed et al. speculate on a possible release of heparin and biologically active basic fibroblast growth factors by degranulation from mast cells also in vivo.

According to a hypothesis developed by Riccardi [5, 23], secretions of mast cells in particular may influence the phenotype and proliferation of local neural crest-derived cells (including neurofibroma, Schwann cells and perineural cells) and/or simply augment the effect of so-called parareceptor membrane components, capable of modulating receptor sites of the cell membrane and thus resulting in the formation of neoplasms.

Interestingly, ketotifen, a benzocycloheptathiophene compound able to block mast cell effects systemically, demonstrated a decrease in the neurofibroma growth in the majority of neurofibromatosis cases when administered orally (2–4 mg/day) for 30–43 months [6, 24].

Neurofibromatosis is a relatively common autosomal dominant trait with a frequency of about 1 in 3,000 [2, 5]. The chance of a coincidental simultaneous occurrence of neurofibromatosis and cutaneous mastocytosis can be estimated as 1 in 3,000,000–24,000,000; this points to a possible association of neurofibroma-like lesions and UP beyond simple coincidence in our case.

Although radiodiagnostic procedures like computed tomography scans are among the further suggested investigations for mastocytosis [1, 9], they seem to have not been applied in every case of UP and neurofibromatosis in the past, which may account for the extremely low number of reported cases with UP and neurofibroma-like lesions.

In conclusion, mast cells may have a causative role in the development of neurofibroma and neurofibroma-like lesions. The existence of neoplasms, including neurofibromas and neurofibroma-like lesions, should be considered when examining UP cases.

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