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Diagnostic difficulties and positive therapeutic response in a patient with sinus histiocytosis with massive lymphadenopathy

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Sir: We have read with interest the paper "Sinus histiocytosis with massive lymphoadenopathy (Rosai-Dorfman disease). Clinicopathological analysis of a paediatric case" by Paulli and colleagues [3]. This case gives us the opportunity to report our experience with a patient affected by the same disease but showing puzzling symptoms mimicking other specific diseases that delayed the diagnosis. Unlike the previously reported case, our patient responded to cytotoxic treatment.

At the age of 7 years, the patient was first admitted to our hospital because of mild neurosensory hearing loss and thyroid enlargement. Hormonal parameters (TSH 13 μu/ml, T3 0.18 ng/dl, T4 2.7 μg/dl) confirmed primary hypothyroidism. Pendred syndrome was tentatively diagnosed and the patient was treated successfully with thyroid hormone. The girl also complained of severe nasal obstruction, nasal phonation and oral breathing, that were attributed to upper turbinate hypertrophy.

At 8 years, the patient manifested diffuse arthritis with joint pain, stiffness and restricted mobility; fever and mild liver enlargement were also detected. Laboratory data supported the inflammatory nature of the process (ESR 125 mm/h, serum IgG 2060 mg/dl, WBC count 11.700/cmm). Serum anti-nuclear antibodies and IgM rheumatoid factor were absent. Juvenile chronic arthritis was diagnosed and the patient was treated with nonsteroidal anti-inflammatory drugs and prednisone. The articular symptoms showed an unpredictable course of exacerbations and remissions.

At 11 years, 1 year after the discontinuation of prednisone treatment, insulin-dependent diabetes developed. The endogenous secretion of glucagon following arginine stimulation was extremely low, suggesting simultaneous damage to islet alpha cells. The patient was treated successfully with insulin.

Three years later, the patient presented with massive orbital swelling due to enlargement of lacrimal glands, proptosis, cervical, submandibular and preauricular lymphadenopathy, hepatomegaly and splenomegaly. A cervical lymph node biopsy showed massive sinus infiltration by histocytic cells with round nuclei and large and pale cytoplasm. They were strongly positive for the S 100 protein on immunohistochemical study. On this basis the diagnosis of sinus histiocytosis with massive lymphoadenopathy was proposed [1, 4].

Abbreviation: CVP = cyclophosphamide, vincristine, prednisone

Treatment with a cytotoxic chemotherapy protocol was started including prednisone, cyclophosphamide and vincristine (CVP) [2]. Five cycles of this regimen were administered and treatment was well tolerated. After the first cycle, the periorbital masses disappeared. The parotid gland and lymph node enlargements and the symptoms related to upper turbinate hypertrophy disappeared following the second CVP cycle; concomitantly inflammatory parameters normalized. Three additional CVP cycles were administered as a consolidation treatment. The articular symptoms have completely cleared, but the thyroid and pancreatic dysfunctions have not improved. The clinical picture is stable after 1 year from the last CVP cycle.

In conclusion, this case report stresses the extreme clinical variability of sinus histiocytosis with massive lymphoadenopathy and provides additional evidence for the efficacy of combination cytotoxic chemotherapy in patients with severe multisystem organ involvement.

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Severe endophthalmitis after neonatal skin lesions with positive cultures of *Aspergillus fumigatus*

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Sir: *Aspergillus* infections are rare in the neonatal period [3]. Disseminated aspergillosis is sometimes accompanied by skin involvement. Granstein et al. [1] reported a cutaneous infection in a preterm infant resulting from *A. flavus* which did not result from disseminated infection. We describe an infant with a severe infection of the skin and positive cultures of *A. fumigatus,* followed by unexpected blindness.

A Caucasian male was delivered vaginally (gestational age: 26 weeks; weight 825 g) and showed signs of respiratory insufficiency, necessitating artificial ventilation for 39 days. On the 10th day after birth he developed a maculopapular rash which became scaly and later pustular. There were no signs of pulmonary infection or other organ involvement. After 1 week, cultures of the pustular cutaneous lesions yielded *A. fumigatus*. Histology with visualization of hyphae was not performed. Bacterial and viral cultures of blood, urine, skin, sputum and the conjuctival swab were sterile. Serologically, concomitant virus infections were not demonstrated. At that moment ophthalmological examination was not performed. The primary skin lesions were treated locally. Broad spectrum antibiotics (flucloxacillin and amoxicillin) were added when pustular lesions developed. After 3 days with broad spectrum antibiotics his clinical condition deteriorated and antifungal treatment (amphotericin B and flucytosine) were started. There was a gradual clinical improvement and the skin lesions healed, indirectly supporting the clinical diagnosis of *Aspergillus* disease. After 4 weeks, intravenous amphotericin B therapy was stopped, without signs of recurrence. Three weeks later during routine ophthalmological examination for retinopathy of prematurity, haziness of the media was seen. Ultrasonography of the eyes showed irregularities of the retina. Vitrectomy was performed and showed a distorted retina with microabscesses. The pus obtained from the vitreous cavity and retinal microabscesses showed no bacterial or fungal growth. Again histological sections were not performed. Thus possible fungal elements could not be looked for. Despite these negative findings a presumptive diagnosis of *Aspergillus* endophthalmitis was made based on the history of the skin lesions with positive cultures of *Aspergillus,* which healed with systemic antifungal treatment, and the known poor intraocular penetration of amphotericin B [3]. The subsequent clinical course was complicated by a patent ductus arteriosus, bronchopulmonary dysplasia and intracranial haemorrhage.

This case shows that in the preterm neonate with a severe or an expanding skin lesion the presence of *A. fumigatus* should be considered. To prove the diagnosis histology is obligatory. Ophthalmological examinations should be performed in preterm infants with suspected fungal infection in order to detect possible fungal endophthalmitis.

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Vancomycin intoxication in a preterm neonate

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Sir: Neonatal bacterial sepsis is associated with a high risk of mortality and morbidity, especially in preterm infants.

Vancomycin therapy is usually started when septicaemia, presumed to be caused by multiple resistant *Staphyloccus epidermidis,* is suspected. At present, there are no data available concerning possible side-effects of vancomycin in the premature neonate, related to serum concentrations. Nephrotoxic and ototoxic side-effects are reported in older children. Ototoxicity is reportedly caused by damage to the sensory cilia in the cochlea and is irreversible. It has been observed with serum concentrations of 80–100 mg/l [1, 2]. The nephrotoxic side-effects in older children are reported to be reversible and related to serum levels > 40 mg/l; the incidence is unknown [1, 3, 4]. We here describe acute vancomycin intoxication in a premature neonate.

A caucasian female was born at a gestational age of 29.3 weeks, weighing 1520 g. In the 4th week of life septicaemia was suspected. Tobramycin (2.5 mg/kg every 18 h) and vancomycin (15 mg/kg every 12 h according to the regimen suggested by Schaad et al.) were started [5]. Blood cultures grew *S. epidermidis*. Twenty-four hours after the start of therapy the child became oliguric and serum creatinine doubled from 41 to 86 μmol/l. Antibiotics were immediately discontinued. Serum vancomycin concentration was elevated (63.3 mg/l 12 h after becoming oliguric) while tobramycin concentration was normal (1.8 mg/l); so we concluded that the renal failure was secondary to vancomycin toxicity. The course of the serum concentrations of vancomycin and creatinine are shown in Fig. 1. During the episode of elevated serum vancomycin concentration no further clinical or biochemical abnormalities were noted. Repeated brainstem evoked auditory potentials showed no cochlear hearing impairment. Two months after the event, no nephrological abnormalities were demonstrated either biochemically or by ultrasonography.

This case suggests that vancomycin overdosage can produce reversible renal impairment in preterm neonates. Creatinine concentration and drug levels should be carefully monitored. If oliguria is observed vancomycin should be immediately withdrawn until serum creatinine and drug concentration are available.

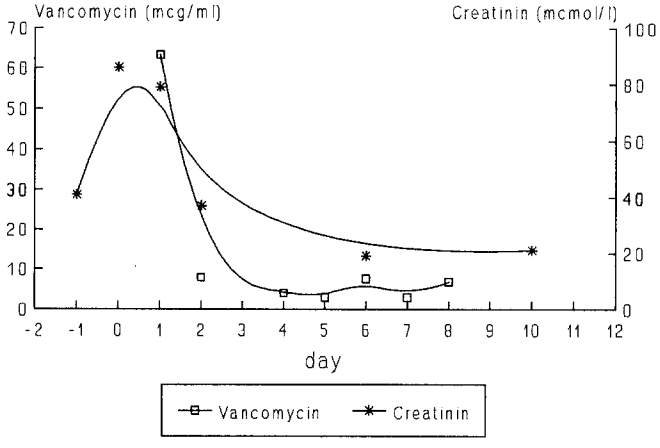

Fig. 1. The course of vancomycin and creatinine serum concentrations in the days before and after vancomycin intoxication

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