Immunohistochemical Detection of Cathepsins in Merkel Cell Carcinomas

Sir,
Numerous in vitro and in vivo studies have shown that proteinases may play an important role in proliferative, invasive and metastasizing processes of malignant cells, particularly because of their destructive effects on the extracellular matrix (1, 2). Possible candidates in these events are metalloproteinases, urokinase-type plasminogen activator and cathepsins (3). The expression of cathepsins is stimulated by tumour promoters, growth factors and second messengers. Many studies have demonstrated high levels of cathepsins in many human tumours associated with tumour cell invasion and metastasis (2). Recently, cathepsin-D expression has been proposed as an indicator of poor prognosis in breast cancer (4).

MATERIALS AND METHODS
We analyzed 4 cases of Merkel cell carcinomas (MCC), immunohistochemically diagnosed by a panel of antibodies (Institute of Pathology, Technical University of Munich). Formalin-fixed paraffin-embedded tissue samples were studied. Five-μm sections were cut, dewaxed, rehydrated and pretreated enzymatically. Then, the sections were incubated with sheep antiserum against cathepsin B (1:100; ICN-Germany) or rabbit antibody against cathepsin pro-L (1:10), as well as against cathepsin pro-D (1:10; both Dianova-Germany). Further, the APAAP-technique described by Cordell et al. (5) was used. Positive reaction was found as a specific red intracellular staining. Control sections were prepared by the absence of the primary antibody.

RESULTS
A positive reaction was found in 2 of 4 cases of MCC for cathepsin pro-L (Fig. 1a) and B as an intracellular diffuse immunostaining. The expression of cathepsin pro-D was also observed in 2 cases of MCC. However, we could detect a paranuclear accumulation of cathepsin pro-D in a few cells of MCC, whereas other cells were negative (data are shown in Fig. 1b).

Fig 1. Immunoreactivity in MCC for cathepsin pro-L as a diffuse intracytoplasmic staining (a) and for cathepsin pro-D as a paranuclear accumulation (b).

DISCUSSION
In vitro studies led to the hypothesis that cathepsins can degrade extracellular components, suggesting that they play an important role in tumour invasion and metastasis in vivo. If cathepsins are related to the invasion of tumours, our findings may explain the aggressive feature of MCC. In fact, clinically, the tumour has a high incidence of local recurrence, and regional and systemic spread. Local recurrence tends to occur within 1 year of excision in approximately one third of cases. No 5-year survival rates are available, since no follow-up data beyond 3 years have been published (6).

Since it fails in therapeutic regimes with a good survival rate, the upregulation of the endogenous inhibitors of cathepsins may be of potential use in this tumour in future. For example, the cystatin superfamily, consisting of stefins, cystatins and kininogens, is a class of natural proteins known to interact strongly but reversibly with cysteine proteinases in vivo (7). Furthermore another potent, reversible inhibitor is the peptide aldehyde, leupeptin, which binds both cathepsin L

REFERENCES
Kawasaki Syndrome or Atypical Measles Mimicking Kawasaki Syndrome?

Sir,

Several infectious agents have been implicated in the pathogenesis of Kawasaki syndrome (KS) (1). Yet its initial definition remains unchanged and is based on clinical arguments (2); severe infectious diseases may then closely mimic KS (3, 4).

CASE REPORT

A 14-year-old boy was admitted for a 15-day illness characterized by high fever (40.5°C), lethargy, non-productive cough, vomiting, diarrhea, angina and polyadenopathy unresponsive to 10 days of macrolide antibiotic therapy. Examination revealed a morbilliform rash on his face and the upper part of the trunk, which had appeared 2 days before admission. Hands and feet were spared. Conjunctivae were erythematous and the lips were fissured. Oral examination showed diffuse stomatitis, without Koplik’s spots, pharyngitis and tonsillitis. The generalized lymphadenopathy included cervical nodes of 2 cm in diameter. Echocardiography ruled out coronary aneurysms, and the treatment consisted of infusions with 2 g/kg globulins (Sandoglobuline, laboratoire Sandoz, Rueil-Malmaison, France) and 3 g/d aspirin. After 2 days fever decreased and the rash extended in a centrifugal manner, with fine desquamation. The boy was discharged on day 7. Medical examinations 1 and 3 weeks later confirmed recovery. Routine blood tests revealed normal initial haemoglobin concentration (148 g/l), discrete anaemia on day 3 (124 g/l), normal leucocyte and platelet counts with T cell ratio CD4/CD8 = 0.68. AST and ALT were slightly raised. Erythrocyte sedimentation rate was 52 mm at 1 h. At the age of 2 he had received attenuated live measles vaccine (Roussel, laboratoire Mérieux, Lyon, France). Viral serology was performed on day 1 at admission prior to the administration of Sandoglobuline and revealed seroconversion to measles virus (ELISA assay, Enzygnost, Behring): presence of IgM titre (with a clear optical density cut-off ratio 8.2) without IgG in acute sera, persistence of IgM and emergence of IgG at 5,200 (arbitrary unit) at the second determination (day 13). Viral culture was not performed. IgM against Epstein-Barr virus, rubella, Parvovirus B 19, cytomegalovirus (by ELISA assays from Abbott, Boehringer, or Biomekonic laboratories respectively) and Antistreptolysins O were negative. IgG against cytomegalovirus and Parvovirus B 19 were positive; late and Waaler-Rose tests were negative.

DISCUSSION

This observation raises two possible diagnoses: KS (possibly measles-related) and atypical measles mimicking KS. First, measles-related KS has to be considered, since this boy had five of the Kawasaki clinical criteria (2): temperature > 38.5°C for 15 days, nonexsudative conjunctivitis, changes of the lips and oral cavity, exanthem and cervical lymphadenopathy. Cases of measles-related KS have previously been reported (5). In our observation prolonged high fever before the rash may be a strong argument for the diagnosis of KS, despite the lack of abnormal blood tests usually associated with KS (1, 4). Secondly, atypical measles may be suspected, because of contemporaneous seroconversion to measles virus and because severe and atypical measles may mimic KS and fulfill enough clinical criteria to be consistent with this diagnosis (3, 4). The seroconversion to measles virus could have been due to a polygenic immune response induced by KS, but the immune responses to other viruses do not support this hypothesis. So-called atypical measles has been reported in young adults who had received killed measles vaccine; clinical presentation includes a rash involving palms and soles and extending in a centripetal manner (3). The rash was different in our patient, and this may run counter to the diagnosis of atypical measles.

It is noteworthy that atypical measles is not infrequent since vaccination coverage has increased (4). A possible decrease in protective antibody rate may explain the atypical presentation. We believe that physicians should keep in mind the possibility of measles when confronted by severe Kawasaki-like rashes, even in vaccinated children, and that a diagnosis of authentic KS is questionable when there are normal routine blood tests.

REFERENCES


Accepted January 9, 1997.

L. Martin1, A. Goudeau1, P. Lanotte2, J. M. Besnier1, G. Lorette1 and L. Vaillant1

1 Departments of 1Dermatology, 2Virology, and 3Infectious diseases, University Hospital, CHU Tours, F–37044 TOURS Cedex, France.

Acute Derm Venereol (Stockh) 77