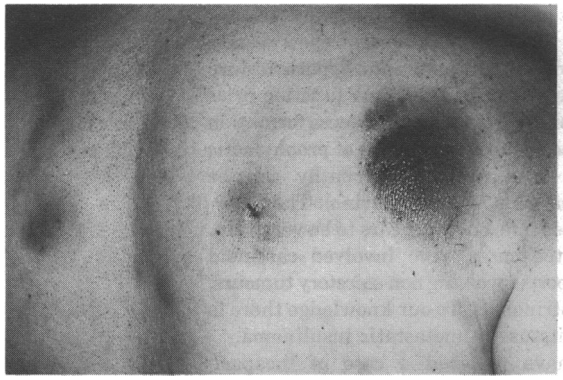

Figure 1. Nodular eruption over back

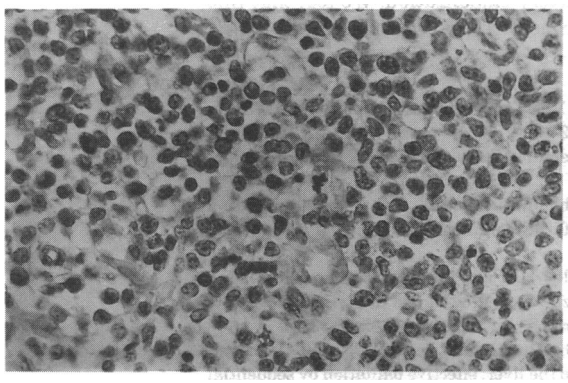

Figure 2. Dermal infiltrate of leukaemia cells

abdominal-pelvic region showed no deep adenopathies. In the light of these results the disease was diagnosed as a malignant non-epidermotropic skin lymphoma with CD4 lymphocytes. In view of the rapid evolution of the lesions and the depth of the infiltrate, chemotherapy (cyclophosphamide and vincristine) was started in association with general corticotherapy. The skin lesions regressed with the first course of treatment. But at this stage changes occurred in the blood count with a rapid increase in circulating monocytes to 3700 mm^3. Serous and urinary lysozyme also increased. Bone marrow aspiration showed a myelodysplastic syndrome. Chronic myelomonocytic leukaemia was diagnosed, and therapy discontinued, particularly as the skin lesions had resolved after three courses of chemotherapy. However, 3 months later, the patient was again suffering from pinkish-brown weal-like lesions on the thorax, coupled this time with generalized weakness and splenomegaly. The blood count showed anaemia (8.5 g/l haemoglobin), thrombocytopenia (70×10^9 l) and neutropenia (1.3×10^9 l). Monocytosis was still in the region of 4000 mm^3. There was slight myelaemia. A new skin biopsy showed identical results. An expanded panel of antisera was then used on this biopsy; the cells were still LEU3 positive, but also reacted positively to anti-HLA Dr (Becton-Dickinson), LEU11 (Becton-Dickinson) and anti-monocyte (Bethesda Research Laboratories). The same staining was observed with circulating monocytes. Treatment was started with hydroxyurea (Hydrea) (500 mg a day) but the patient became gradually weaker, splenomegaly increased and a bone marrow showed acute myelomonoblastic leukaemia. The patient died a month later.

Discussion

There are two points raised by this observation. Firstly, specific skin involvement in chronic myelomonocytic leukaemia would appear to be exceptional. We have found reports of only 10 cases in medical literature of such lesions which can take the form of nodules, a pruriginous rash or a maculo-papular eruption[2-5]. In each case the biopsy showed a non-epidermotropic dermal infiltrate composed of mononuclear cells. Occasionally, as was the case with our patient and the three cases reported by Copplestone[5], these lesions are the first symptom of haemopathy. When they occur in the course of the disease, prognosis is variable. They can herald an acute phase of the disease, but in other cases no deterioration of the patient's condition is reported.

The second point concerns the use of monoclonal markers. It is certain that it was the positive reaction with antisera to LEU3 which is the usual observation for CD4 lymphocytes that led to the diagnosis of lymphoma. However, this antibody is equally reactive with cells of the monocyte-macrophage lineage[6]. Screening the second biopsy with an expanded panel of antisera enabled us to confirm the origin of the cells composing the infiltrate. This would show how important it is to use immunohistochemistry in haemopathic skin infiltration but on condition that the screening panel of antisera be sufficiently large to allow clear interpretation and to avoid errors due to cross-reactions.

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Correlation between serum oncogene protein expression and the development of neoplastic disease in a worker exposed to carcinogens

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Evidence suggests that oncogene activation may be a relatively early step in the carcinogenic process and that the detection of oncogene activation may be a useful marker for identifying individuals at risk for cancer[1]. The case reported provides evidence in support of this hypothesis.

Case report

A previously described cohort of 24 workers with known exposure to carcinogenic materials was referred to Columbia-Presbyterian Medical Center in New York for evaluation[2]. These individuals were screened for the presence of proteins in their serum encoded by nine different oncogenes using a recently developed assay[2,3]. One 57-year-old white male in this cohort was of particular interest because of his long history of workplace exposure to asbestos, pesticides and polychlorinated biphenyls. He had also smoked 20 cigarettes

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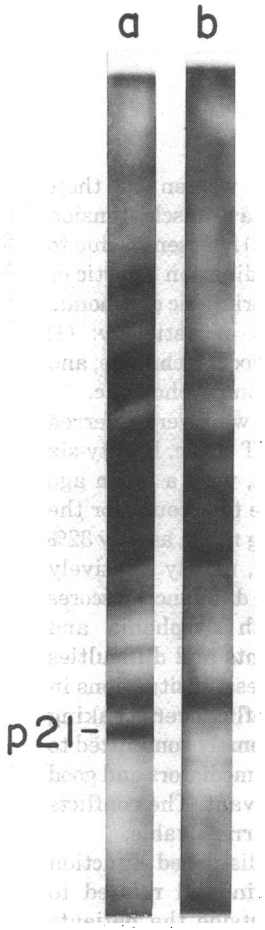

Figure 1. Serum immunoblots of the patient probed with a monoclonal antibody directed against the peptide sequence of the H-ras oncogene by the method described in ref. 2, (a) 18 months prior to clinical manifestation of the colonic polyp, and (b) 6 weeks after removal of the polyp. Note the presence of the band for the H-ras encoded p21 protein in (a) (dark band indicated by p21) which is not seen in (b). Additional bands present in (a) but not in (b) correspond to $p55^{ras}$ and $p100^{ras}$ bands as defined in ref. 3; other bands represent non-specific banding patterns present in all serum (see ref. 2)

a day for many years. Laboratory evaluation was remarkable for a marked elevation of serum proteins encoded by the H-*ras* oncogene (see immunoblots Brandt-Rauf and Niman[2] and Figure 1a). The patient had no evidence of neoplastic disease at that time. However, approximately 18 months later, he developed rectal bleeding due to a tubulo-villous adenoma of the colon. Six weeks after removal of the adenoma, the patient's serum oncogene proteins were found to have reverted to a normal pattern (Figure 1b). On this basis, it was presumed that the source of this patient's serum *ras* protein was the adenoma and that the oncogene protein produced by the adenoma was detectable in his serum 18 months prior to the onset of clinical manifestations of the disease. Unfortunately, this conclusion must remain presumptive; due to the unavailability of sufficient appropriate tissue for definitive confirmation of increased oncogene protein in the adenoma itself, there is no direct evidence that the source of elevated H-*ras* p21 in this patient's serum was the adenoma.

Discussion

This patient did not report any exposure to carcinogens known to activate the *ras* gene, except for benzo(a)pyrene from cigarette smoking, but this has not been associated with colonic neoplasia. On the other hand, this patient did have a long history of exposure to asbestos, which has been implicated in the development of colorectal cancer[4].

The *ras* gene can be activated by at least two mechanisms, point mutations or over-expression of the proto-oncogene. Asbesto has been found not to exhibit mutagenic activity in in vitro assays. However, several investigations have identified pathogenetic mechanisms by which asbestos could produce oncogene activation by over-expression. Studies have shown that asbestos fibres are clastogenic to cells in culture[5,6], and chromosome breakage and rearrangement has been shown capable of causing activation by over-expression of certain oncogenes[7]. Alternately, more recent studies have shown that asbestos fibres are capable of transfecting exogenous DNA segments, including oncogenes and promoter sequences, into primate cells in culture and producing cell transformation[8]. Thus, it is possible that asbestos could introduce additional copies of a proto-oncogene into cells and/or could introduce promotional regulator sequences into cells, which in both cases could lead to gene over-expression and an oncogenic effect. Thus, in this individual, one could hypothesize that prolonged exposure to asbetos produced (by one of these mechanisms) increased expression of the *ras* proto-oncogene in his colonic epithelium. This was manifested by increased quantities of the proto-oncogene encoded p21 protein in his serum. Ultimately, the proto-oncogene over-expression led to colonic neoplasia, in this case an adenoma which was identified clinically prior to its progression to a malignant growth; colonic adenomas have been identified as being capable of over-expression of the *ras* gene[9]. With the subsequent excision of the adenoma, the source of the increased amounts of the *ras*-encoded p21 protein was removed, and p21 protein was no longer detected in the patient's serum.

This case points out the potential utility for oncogene protein products as markers for the early detection of oncogenic changes. Further prospective studies are underway to confirm the predictive value of this approach for early cancer detection and prevention.

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