Correspondence and Short Communications

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MULTIPLE MYELOMA—TRANSFORMATION TO HIGH-GRADE MALIGNANT LYMPHOMA

Sir – The development of high-grade malignant lymphoma in a patient with chronic lymphocytic leukemia was first reported by Richter in 1928 (10).

Transformation to high-grade malignant lymphoma is now a well-known event in other low-grade malignancies of the B cell lineage, such as nodular lymphoma (4) and has recently been described also in hairy cell leukemia (5). The occurrence of a similar terminal aggressive development has been described also in multiple myeloma, but seems to be less well-known. In 1973 Holt & Robb-Smith described 3 patients with myeloma who developed soft-tissue masses, consisting of poorly differentiated cells, after apparent successful cytotoxic treatment (8). In 1981, Suchman et al. reported 7 myeloma patients who were characterized by rapidly enlarging soft-tissue masses with histologic features similar to those of large-cell lymphoma (13). One previous report deals with the results of immunologic examination of tumor cells from a similar patient in whom the soft-tissue tumor cells contained immunoglobulin of the same class as the bone marrow myeloma cells (14).

We have seen myeloma patients whose disease ran a course similar to that described in the above mentioned papers. The intention of the present report is to propose, that the term transformation should be applied to cases like these. Knowledge about this condition and its identification is a prerequisite for the development of innovative therapy in multiple myeloma transformed to high-grade malignant lymphoma. This report has been restricted to one patient only, due to the belief, that this case is a representative example of transformation of the malignant myeloma cell clone to high-grade malignant lymphoma of immunoblastic type. Also, the lymphoma in our patient seemed to respond to treatment with high-dose cytosine-arabinoside, a treatment model never attempted in similar cases previously as far as we know.

Case report. A 46-year-old male was initially seen with back pain, chest pain, and fatigue. On examination he seemed acutely ill and slightly confused. The chest was tender. Laboratory examination showed anemia, with a hemoglobin value of 8.3 g per dl. The serum calcium was high, 3.7 mmol per l (148 mg per l), and the serum creatinine was elevated, 331 μmol per l (32 mg per l). Monoclonal IgG, 5.4 g per dl, was present in the plasma, and a urine sample contained 0.5 g kappa chains per l. A bone marrow aspiration biopsy showed 33% small plasma cells and lymphoplasmacytoid cells (Fig. 1). A skeletal x-ray survey showed numerous osteolytic lesions. A diagnosis of myeloma stage III B according to Durie & Salmon (7) was made, and the patient was treated with plasmapheresis and chemotherapy (vincristine, BCNU, cyclophosphamide, melphalan, prednisone) according to the M-2 protocol (3). His condition improved rapidly. Four months later the M-component had disappeared, and a bone marrow biopsy was normal. Chemotherapy was discontinued after 10 months.

Fifteen months after the initial visit a cervical vertebra collapsed, but the bone marrow was still normal with less than 2% plasma cells and total IgG only 12 g per l so he was only treated with local radiotherapy. However, one month later there was a progression of lytic destructions in the pelvis and the skull, but the bone marrow still contained less than 2% plasma cells. Chemotherapy according to the M-2 protocol was reinstituted, but his condition grew worse; after 2 cycles of treatment he developed hypercalcemia, and chemotherapy was switched to continuous infusions of vincristine and doxorubicin with high-dose prednisone (VAD) according to Barlogie et al. (1). Three cycles of VAD were administered, the bone pain improved and serum calcium was normalized.

Twenty-two months after the initial visit his condition deteriorated rapidly, in spite of on-going VAD treatment. A bone marrow biopsy was normal. Severe progression of lytic bone lesions was seen and he developed a partial paraparesis. Treatment was now started with recombinant alfa-interferon. No improvement was seen after one month of treatment, so interferon treatment was stopped.

Twenty-three months after the initial visit he developed a rapidly growing subcutaneous tumor on the left shoulder. At the same time he became confused, without concomitant hypercalcemia or fever. A cytocentrifuged cerebro-spinal fluid sample contained a normal number of leukocytes and normal-appearing lymphocytes. Electrophoresis and immunofixation of cerebrospinal fluid demonstrated a protein pattern similar to that of plasma. The plasma IgG M-component was unchanged; total IgG 15 g per l. A bone marrow biopsy showed 1–2% plasma cells. Aspiration biopsies from the shoulder tumor showed cells with an immunoblastic morphology (Fig. 2). Numerous mitoses were observed. By immunoperoxidase technique it was demonstrated, that the cells contained IgG kappa immunoglobulin, predominantly located at the cell surface (Fig. 3). The patient was now treated with cytosine-arabinoside 2 g twice daily for 4 days. The tumor disappeared rapidly, but the patient died 2 weeks later in Candida septicemia. Autopsy showed disseminated Candidosis in multiple organs, even in the myocardium. There was lymphomatous engagement of the left pleura, and multiple small bleedings were seen in the cerebrum.

Discussion. About 10% of patients with monoclonal gammopathy of undetermined significance (MGUS) develop multiple myeloma during a median follow-up of 10 years (9). In a retrospective study of patients with stage III multiple myeloma, 28% had a known stage I myeloma for a median of 35 months before entry into stage III (15). The median survival time for those patients after their entry into stage III was virtually identical to that of patients not diagnosed until stage III (15). These findings are compatible with the theory of a step-wise series of events, ultimately making the initially small and low-malignant clone of

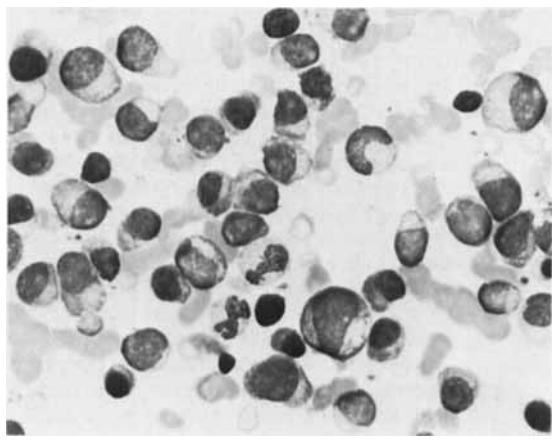

Fig. 1. Giemsa-stained bone marrow smear with ordinary bone marrow cells and a significant proportion of small and medium sized plasma cells. Magnification ×525.

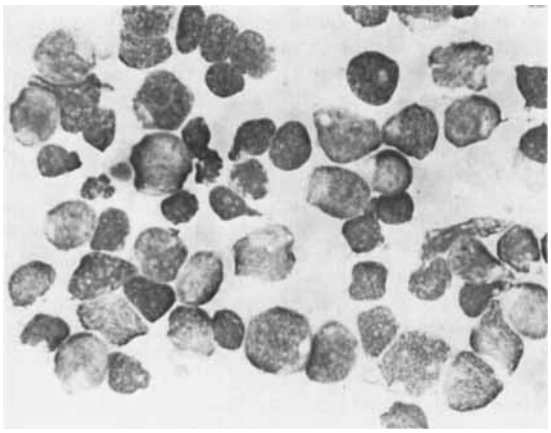

Fig. 2. Fine needle aspiration biopsy from soft tissue tumor showing predominance of often poorly preserved, relatively large blastic cells. Giemsa-staining. Magnification ×525.

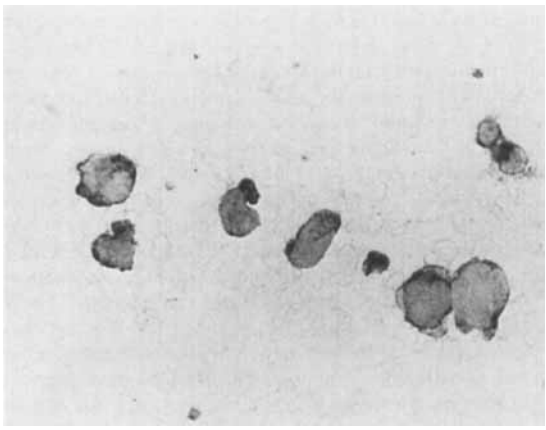

Fig. 3. Cytospin preparation of cells obtained by fine needle aspiration biopsy from soft tissue tumor and stained for kappa light chains. Peroxidase-antiperoxidase technique. Magnification ×525.

cells which constitute the MGUS-condition, to terminate in stage III myeloma. However, the speed by which these events take place varies widely between individual patients. There is convincing evidence for such a step-wise evolution of the malignant clone towards more aggressive behavior in other hematological neoplasms, such as chronic myelogenous leukemia (11). The possibility of an evolution of new clones of myeloma cells within the original clone has been discussed by Durie et al. (6).

A substantial proportion, one third of treated myeloma patients, develop an aggressive terminal phase, as shown by Bergsagel et al. (2). Suchman et al. described 7 myeloma patients who were treated with alkylating agents and developed soft tissue tumors morphologically indistinguishable from large-cell lymphoma (13). Median survival after the appearance of such tumors was only 4 months. The patients had cerebral symptoms thought to be caused by fever or hypercalcemia. Most patients were males and younger than myeloma patients use to be. Interestingly, the lymphoblastoid cells were not found in the bone marrow, which contained a remarkably low percentage of plasma cells in several cases. The low plasma cell content of the bone marrow corresponds to reports about decreasing M spike with increasing tumor burden in multiple myeloma (12).

The patient reported here was male and relatively young, like the patients of Suchman and co-workers. The myeloma responded well to initial chemotherapy but became later more aggressive with poor response to therapy. In spite of the obvious clinical deterioration, the bone marrow remained normal and the M-component small. Like the patients of Suchman et al. he developed a subcutaneous lymphoma, which in our patient was shown to consist of immunoblasts, bearing immunoglobulin of the same heavy and light chain classes as the myeloma. This finding supports, but does not prove, the opinion that the lymphoma evolved from the myeloma. The subcutaneous lymphoma responded to therapy with high-dose cytosine-arabinoside, but the patient died in Candida septicemia during pancytopenia.

Multiple myeloma was described as a disease entity already in the 18th century. Why has transformation not been observed until recently? One reason might be that most patients with advanced myeloma died within a few weeks or months after diagnosis before the melphalan era. During the last decade, patients with advanced myeloma survive longer, due to intensified chemotherapy and improved supportive care. It seems probable, that this prolongation of survival times has permitted the development, and increased the chance of observing transformation of multiple myeloma to high-grade malignant lymphoma. Another possibility would be that cytotoxic treatment per se may promote transformation. Interestingly, transformation from MGUS or stage I myeloma into high-grade malignant lymphoma has not been reported. One explanation is that the development of immunoblastic lymphoma requires several steps, making the transition directly from benign-phase monoclonal plasma cell disorder to large-cell lymphoma unlikely. However, studies performed by Durie & Grogan show that a proportion of untreated myelomas with a very aggressive clinical disease and short survival are characterized by immature phenotype and CALLA-positivity (6). This important observation shows that previous chemotherapy is no prerequisite for this phenomenon. Also, this observation indicates that some myelomas may have evolved into different subclones, some of which are more resistant to chemotherapy and more primitive, already at the time of myeloma diagnosis.

One reason for the low number of reports dealing with transformation in myeloma is, that this event might be underdiagnosed. Its diagnosis requires knowledge of this possibility, leading to biopsy from the tumor. Thus, transformation into immunoblastic, high-grade malignant lymphoma, may be considerably more common than generally known. Anyhow, the results of conventional myeloma chemotherapy in such cases are disappointing. Although treatment with high-dose cytosine-arabinoside was also unsuccessful in our patient, there was a response to treatment, indicating that high-dose cytosine-arabinoside should be tested in a larger number of patients.

Key words: Multiple myeloma, high-grade malignant lymphoma, transformation.

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GARDNER'S SYNDROME AND THYROID CANCER—A CASE REPORT AND REVIEW OF THE LITERATURE

Sir—Gardner's syndrome (GS) is a familial condition consisting of adenomatous polyposis coli, mandibular osteomas and soft tissue lesions (6, 8). If the polyposis is not treated an adenocarcinoma of the colon develops in almost 100% of the cases at an unusually early age. In about 20% of the cases polyps are also detected in the periampullary region and may undergo malignant degeneration (7). Endocrine neoplasms have also been noted, specially thyroid cancer, both before and after the diagnosis of polyposis coli (2, 13).

In the present paper, a patient with GS and follicular carcinoma of the thyroid is reported and discussed. The case was discovered during a survey of a family with GS detected in 1983 in the province of Trento in northern Italy.

Case report. A 24-year-old woman (Figure) was first examined at the Surgical Department of the S. Chiara Hospital of Trento in November 1983. On December 3, 1983, the patient underwent total colectomy with ileo-rectal anastomosis because of adenomatosis coli. Radiograms of skull and mandible were normal as well as endoscopy and double contrast roentgen examination of the gastro-duodenal tract. The patient had supranumerary teeth. A diagnosis of GS was made.

At a second examination, performed at the Oncologic Department in September 1986, a solitary left-sided thyroid nodule, 10 mm in diameter, was discovered. The patient had never been exposed to ionizing radiations to head and neck. Two of her ancestors had died because of tyroid cancer, one papillary carcinoma (III-9, Figure) and one cancer with unknown histology (I-2, Figure). Thyroid function tests were normal. Thyroid scanning with $^{99}Tc^{m}$ pertechnetate revealed a 'cold' nodule in the lower third of the left lobe. Ultrasonography showed this nodule as a solid mass 6×12 mm, slightly less echogenic than normal thyroid tissue. Another smaller nodule (3×4 mm) was also detected in the upper third of the left lobe. Fine needle aspiration for cytologic examination of the first mentioned nodule revealed numerous non-cohesive epithelial cells of follicular type with slight cellular atypia.

On October 30, 1986, the patient underwent total thyroidectomy. The specimen revealed a well differentiated multicentric follicular carcinoma without invasion of the capsule. At present, the patient is well.

Patients with GS are at risk for a variety of extracolonic benign and malignant lesions which can occur both before and after the discovery of the colonic adenomatosis (13). A careful long-time observation is therefore necessary. The actual incidence of endocrine neoplasms in GS is unknown because these may be non-functioning or occult (12). Only autopsy studies on series of patients with GS could answer this question. Thyroid cancer is the most frequent endocrine neoplasms reported in such patients. In the literature 17 cases have been reported, including our own case (Table). The thyroid cancers have usually been detected in the third decade of life and the female–male ratio is 4:1. In most cases the tumors have been multicentric and papillary. In two thirds of the reported cases for which information was available, carcinoma of the thyroid preceded the detection of colonic polyposis with 7 to 10 years (3–5, 10, 14, 15). In our patient the thyroid cancer was detected after the diagnosis of polyposis coli and similar cases have been reported previously (5, 9, 11, 13, 16).

The cumulative incidence rate of thyroid cancer in the studied family (43 living members during the first four years of survey) was 2.32%. In the same period (January 1, 1983–December 31, 1986), the corresponding incidence rate of thyroid cancer in the general population of the Trento province (about 420000 inhabitants) was 0.014%. The relative risk of thyroid cancer among members of the GS family was thus 165. This high risk strongly supports the use of a screening program for detection of thyroid cancer in GS families and specially in patients with manifest GS. According to Thompson et al. (16) ultrasonography could be used as a screening instrument as it is simple, rapid, innocuous and cheap and has a higher resolution than thyroid radionuclide scanning (17). An extensive application of thyroid ultrasonography should also allow a better assessment of the frequency of thyroid disorders in GS and GS families.

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