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LETTER TO THE EDITOR

Gastric Adenocarcinoma in a Patient Under Immunosuppressive and Omeprazole Treatment

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Sir,

A 58-year-old man, heart transplant recipient, was admitted to our hospital with a 3-month history of flatulence and a 2-week history of epigastric pain and vomiting after meals. He had undergone heart transplantation 18 months previously because of end stage left ventricular failure caused by coronary heart disease and since then he was put on cyclosporin 2.67–4 mg/kg daily, azathioprine 0.34–0.67 mg/kg daily, prednizolone 5 mg daily and omeprazole 40 mg daily.

There was a history of melaena 3 years before due to duodenal ulcer as shown by barium upper GI tract radiographs. The patient underwent 6 weeks of successful antiulcer therapy and was free of symptoms thereafter.

His present examination showed epigastric tenderness and nodular enlargement of his liver 10 cm below the right costal margin. Laboratory tests showed high sedimentation rate 110 mm/h, low haemoglobin, haematocrit and iron levels 9.7 g/dl, 30.9% and 27 μg/dl respectively, high lactate dehydrogenase and γ-glutamyl transpeptidase levels 338 IU/1 and 157 units/1 respectively, normal aminotransferases and globulins and therapeutic levels of cyclosporine (200 ng/ml). Gastroscopy revealed a neoplastic growth in the lesser curvature of the stomach. Biopsy and histologic examination of the lesion confirmed the diagnosis of adenocarcinoma of intermediate differentiation, enteric type (according to Lauren classification). Liver ultrasonography, scanning and computerized tomography showed multiple liver metastases. The patient underwent unsuccessful chemotherapy and died 6 months later. Taking into account that the natural history of gastric cancer is that of a slowly progressive neoplasm which may take 3 to 4 years from 'early' to advanced disease,[1] the possibility of the existence of an early stage gastric carcinoma prior to heart transplantation cannot be neglected. The lack of related symptoms and radiographic findings (as mentioned above) in combination with the close clinical and laboratory follow-up due to ischaemic heart disease makes the possibility of misdiagnosis rather unlikely.

Therefore two questions from this case remain to be answered: could immunosuppressive treatment alone be related to this event or was it a concomitant effect of immunosuppression and omeprazole treatment?

Several retrospective studies in the literature relate the use of immunosuppressants with the development of malignancies including lymphomas, skin neoplasms, colon adenocarcinoma and liver[2] and tongue neoplams.[2–8] The interval between exposure and appearance of these events varies from 16 to 33 months.[2,3]

The incidence of the events also varies in these retrospective studies from 3.1%[2] to 8.1%;[4] while the relative risk of developing a neoplasm or a lymphoma among 478 recipients under immunosuppressive treatment is reported to be 3.08 and 26.9, ($p < 0.005$) respectively.[3]

Animal findings indicate that either immunodeficiency- or immunotherapy-induced[8] suppression of T lymphocyte activity[9] may enhance tumour progression but long-term exposure to an immunodeficient environment is necessary for

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tumour progression of Epstein Barr positive human lymphoid cells.[10] Animal models of liver metastasis from colon adenocarcinoma have also shown aggravation of the metastatic lesion in the presence of cyclosporin,[11] while combinations of various immunosuppressants with associated 'over-immunosuppression' may result in a higher incidence of viral infection and malignancy.[12]

On the other hand, long-term gastric acid suppression has been implicated with the development of neoplasia of the gastric mucosa in rodents.[13] Hypergastrinaemia or the presence of other unidentified trophic factors for the gastric mucosa, bacterial colonization and subsequent generation of carcinogenic substances have been proposed as triggering events,[13–15] while direct damage to cellular DNA due to omeprazole is another option.[16] Even though such observations have not been confirmed in humans[17,18] because of lack of long-term follow-up studies, we assume that co-administration of immunosuppressive therapy poses an additional risk for the development of gastric cancer. The exant role of each of the drugs in the present case (cyclosporine, azathioprine, omeprazole) for the development of carcinogenesis is for the time being difficult to evaluate but it seems reasonable to suggest that increased caution seems justified when such drug combinations are used.

In conclusion, the avoidance of long-term potent antisecretory therapy for patients under immunosuppression when other therapeutic modalities are regarded as equally effective is for the time being a wise approach.

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