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Case report

Pancreatic cancer as a second tumour following treatment of Hodgkin's disease

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Abstract. Over the past 30 years, the life expectancy in patients with Hodgkin's disease has greatly improved. However, adverse long-term side-effects are now well recognized and development of second malignancies is one of the most important. We report the case of a patient who developed pancreatic cancer 9 years after treatment, with chemotherapy and radiation, for Hodgkin's disease. The increasing number and variety of solid tumours after curative treatment of Hodgkin's disease points to a need for new, less toxic regimens.

Introduction

The life expectancy of patients with Hodgkin's disease (HD) has improved dramatically over the past 30 years. With advances in treatment of HD, the expected cure rate is approximately 85% [1].

However, with improved survival has come the recognition of adverse long-term events, the most important of which is the occurrence of second malignancies. Several studies report a significantly increased risk of certain solid tumours, especially breast and lung cancers [2–7]. Although gastrointestinal tumours have also been described, very few pancreatic cancers have been reported as second malignancies after treatment of Hodgkin's disease [3–5].

We present here the case of a patient who developed a pancreatic cancer 9 years after treatment for Hodgkin's disease, both to document this unusual occurrence and to highlight the need for long-term follow-up of these patients.

Case history

A businessman was diagnosed in 1981 at the age of 44-years-old with Hodgkin's disease, Stage IIIA. He presented with mediastinal and hilar lymphadenopathy, as well as enlarged paraaortic lymph nodes. The spleen was slightly enlarged. The liver was normal. Bone marrow aspiration and biopsy were negative. The diagnosis was confirmed by mediastinoscopic biopsy which revealed Hodgkin's disease, mixed cellularity type.

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The patient received six cycles of MOPP and achieved complete regression of the mediastinal and hilar lymphadenopathy. However, because of the persistence of a palpable spleen, he underwent laparatomy for splenectomy and liver biopsy; no residual disease was found. The patient received three further cycles of MOPP and was considered disease-free. In 1984, a routine chest X-ray demonstrated a mass at the right hilum, suggestive of lymphadenopathy. Investigations, including CT scans of chest, abdomen and pelvis as well as bone marrow biopsy, revealed recurrent disease limited to the right and left hilar. He received treatment with external beam radiotherapy.

A dose of 35 Gy was delivered with a daily dose of 1.75 Gy, 5 days a week over 4 weeks, to a mantle field. An additional dose of 7 Gy was given to the mediastinum in four daily fractions. Subsequently, the paraaortic nodes and splenic pedicle were also radiated at a dose of 35 Gy in 20 treatments over a period of 4 weeks. Both mantle and paraaortic with splenic pedicule fields were treated with an anterior and posterior equally weighted field arrangement. A 4 MV photon beam was used and all radiation fields were treated daily. The patient had no evidence of residual disease on completion of treatment.

In January 1993, at the age of 55-years-old, the patient complained of upper abdominal pain, anorexia and weight loss of about 25 pounds. Physical examination was unremarkable except for cachexia. The abdominal CT scan showed a mass in the paraaortic region at the level of the upper pole of the left kidney (Figure 1). Laparotomy revealed an unresectable mass in the body of the pancreas. Biopsy showed an adenocarcinoma compatible with a primary pancreatic carcinoma.

The patient was treated with combined external beam radiation and 5 FU according to the

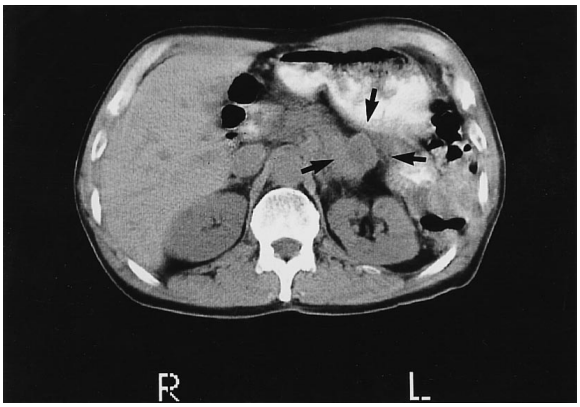

Figure 1. Axial CT section showing a mass in the left paraaortic region.

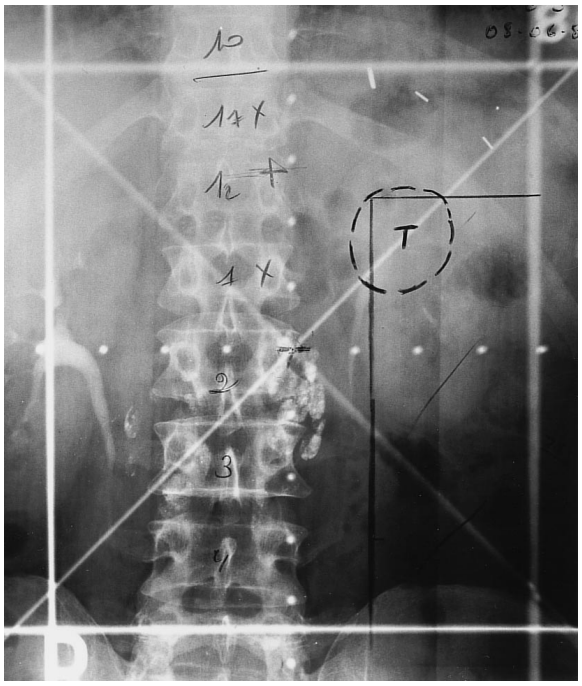

Figure 2. Simulation film of the paraaortic region and splenic pedicule showing approximately where the pancreatic cancer (T) arose.

Gastrointestinal Tumour Study Group (GI 9173) protocol [8]. He received two courses of external beam radiotherapy of 20 Gy each separated by an interval of 2 weeks, combined with weekly injections of 5 FU, 500 mg m^{-2} by intravenous bolus. Oblique radiation fields were used to avoid excessive irradiation to the spinal cord, kidneys and gastrointestinal tract. 1 month after completion of radiotherapy, an abdominal CT scan showed 40% shrinkage of the pancreatic tumour.

During the 2–3 months following his treatment, the patient experienced slight improvement of his general condition with better appetite and less fatigue; however, his condition deteriorated rapidly. He was finally admitted with shortness of breath and chest pain and was found to have a pneumothorax. He died a few days later, 8 months after the diagnosis of his second malignancy.

Discussion

Radiation is a known carcinogen. However, to characterize a human solid tumour as radiation-induced, certain criteria must be fulfilled [9]. Clearly, the tumour must occur in the irradiated field, appear after a period of latency, usually a decade or more, and be histologically distinct from the previous neoplasm. In large series, it is necessary to demonstrate that tumours occur with a frequency significantly greater that in the population at large.

In our patient, the pancreatic carcinoma was judged to arise at the margin of the irradiated field (Figure 2) 9 years after treatment. Few cases of pancreatic carcinoma after Hodgkin's disease have been reported. In their study, Abrahamsen et al report two cases of pancreatic cancer and estimate the absolute risk per 1000 person/years at 0.23 [6].

The development of second malignancies after treatment for Hodgkin's disease is now well established [2,4,5,10,11]. Although the association between solid tumours and treatment-specific risk is not as strong as with leukaemia, several studies have reported that patients receiving radiotherapy have a significantly higher risk of developing solid tumours, than those receiving chemotherapy alone [2–6]. Lung and breast cancers appear to be the most frequent second solid tumour.

Some studies on second malignancy in HD evaluated the relationship between solid tumours and radiation fields. Birdwell et al reported that 60% of the gastrointestinal cancers arose within or at the margin of the radiation field [12] and in a study from the Norwegian Cancer Registry this figure was 46% of all solid tumours [6]. Some data regarding dose–response relationships from radiation-induced cancer are available from studies of secondary thyroid cancer. At low doses the relationship appears to be linear [13]. From the Late Effect Study group, Tucker et al found a large increased risk of thyroid cancer from radiation doses greater than 2 Gy compared with doses less than 2 Gy, but found a relatively flat dose–response curve at higher doses [14]. However, a study of 150 000 patients treated for cervical carcinoma with doses of several hundred gray, reported an increased risk of cancer of the bladder, rectum and vagina. A dose–response gradient was observed reaching a fivefold increase for doses greater than 150 Gy for all female genital cancer taken together [15]. The authors of one review concluded that radiation is associated with an increased incidence of secondary malignancy, both in heavily irradiated target tissues and in more remote organs that receive few gray [15].

Numerous studies have shown a strong association between intensive chemotherapy and leukaemia among Hodgkin's disease patients. However, the role of chemotherapy in the development of solid tumours remains unclear. Most studies do not show a significant increased incidence of solid cancers after chemotherapy alone. Tucker et al reported that the risk of developing solid tumours appeared higher after adjuvant chemotherapy and irradiation, than after radiotherapy alone but the difference was not significant [4]. The same conclusion was reached by Boivin et al [3]. However, it is of note that, in general, the duration of follow-up is shorter for patients treated with chemotherapy or with combined modality treatment than for patients treated with radiotherapy. Boivin et al reported that the recurrence rate of solid tumours following chemotherapy was 1.4 (95% CL: 1.1 to 1.8) in a recent case cohort study on 10 472 patients conducted between 1940 and 1987, with long duration of follow-up [16].

Several studies have clearly shown that the risk of second malignancies increases with time and this is mostly due to solid tumors [2,4,6]. The mean cumulative risk of all second malignancies reported by Abrahamsen et al was 14.4% at 18 years. Most of the risk was due to solid tumours with a steady increase in cumulative risk to 11.2% at 18 years. These results correlate with those published by Tucker et al, where the mean 15 year actuarial risk of all second cancers was 17.6%, of which 13.2% were solid tumours. This is in contrast with the risk of leukaemia which reaches a peak in the early years of exposure but declines greatly beyond 10 years [4–6,17]. In their analysis of the occurrence of second tumours among 192 patients with Hodgkin's disease with a median follow-up of over 15 years, Blayney et al reported no case of acute leukaemia more than 11 years after treatment [17].

Pancreatic cancer as a second malignancy has been reported following testicular cancer, in which irradiation therapy was the main treatment [18–20]. A recent study of 6187 men treated for testicular cancer in Denmark showed significant increased incidence of pancreatic carcinoma with relative risk of 2.3 [18]. The greatest incidence was seen 10–19 years after treatment.

There is enough evidence now that intensive radiotherapy and chemotherapy for treatment of HD significantly increases the risk of second malignancies. Follow-up of these patients is essential to document all second malignancies and to accumulate a large volume of evidence that will allow accurate predictions of the relative risk of solid tumour second malignancies according to site and histology.

Although the high cure rate of HD with current treatment far outweighs the risk of second cancer, it is clear that the development of new treatment strategies with equivalent efficiency but less toxicity is an important goal in the management of patients with this disease.

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