Case Report

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Second Gastric Cancer After the Treatment of Primary Stomach Diffuse Large B-Cell Lymphoma

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Abstract

We report a case of gastric carcinoma occurred 11 years after treatment of gastric lymphoma in a 38-year-old patient with a review of the literature.

Keywords: Gastric lymphoma; Second primary cancer; Stomach cancer; *Helicobacter pylori*; Radiotherapy

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Introduction

Adenocarcinoma and lymphoma are the two most common malignant tumors of the stomach [1,2]. The occurrence of second cancer after the treatment of gastric diffuse large B-cell lymphoma is rare [1,2]. We report a case of gastric carcinoma occurred after the treatment of gastric lymphoma with a literature review.

Case Report

A 38-year-old man was consulted at our hospital in 2002 with epigastric pain, vomiting, weight loss and fatigue. There was no evidence of lymphadenopathy.

Gastroscopy demonstrated an ulcerative lesion of the stomach and pyloric stenosis. Biopsies showed a diffuse large B-cell lymphoma. It was described as a large-sized lymphoid cells presenting scant cytoplasm, large nucleus and associated with matures lymphocytes. Immunohistochemistry revealed positivity of the lymphoid cells to CD20, CD79a and Bcl-2.

The bone marrow was not involved. Initial laboratory study, especially lactate dehydrogenase was normal. No lymphadenopathy was observed in cervical, thoracic, abdominal and pelvic computed tomography. Thus we classified the disease as stage IE.

The patient underwent 3 cycles of CHOP chemotherapy (Cyclophosphamide, Doxorubicin, Vincristine and Prednisone). Gastroscopy and Biopsies confirmed the complete remission of the lymphoma. He was then treated with radiation therapy of the whole stomach (40 Gy up to February 2003).

After the treatment, he was in complete remission. He was followed by clinical exam, endoscopy and biopsies.

In 2014, he consulted for vomiting. Physical examination revealed an abdominal pain and all laboratory tests were normal. Gastroscopy revealed mucosal infiltration of the antrum with pyloric stenosis. Biopsy and Histopathological examination demonstrated the presence of gastric indifferencieded adenocarcinoma with signet ring cell component. The cervical, thoracic, abdominal and pelvic computed tomography showed circumferential wall thickening antero-pyloric without peri-gastric or lymphadenopathy involvement. The patient had total gastrectomy with D2 lymphadenectomy. The final pathologic examination demonstrated a poorly differentiated

adenocarcinoma with signet ring cells of the antral wall infiltrating the muscular and extended to the duodenum. The tumor was classified pT2N1M0. He had adjuvant chemotherapy (LV5FU2 cisplatin up to September 2014). Eighteen months after the surgery, the patient is alive in complete remission.

Discussion

The incidence of gastric adenocarcinoma was higher in patients treated for gastric lymphoma than the general population with a relative risk of 6 [3-5]. If gastric cancer occurred in patients treated for the same location, lymphoma is considered a second primary cancer. Indeed, a second primary cancer (SPC) is defined as a new invasive primary tumor diagnosed in a person already affected by cancer and who is not a recurrence or metastasis, or multifocal or multicentric cancer [6,7].

The etiologic factors in these SPC is a young age at diagnosis, the combination of chemotherapy, the infection with *Helicobacter pylori* (HBP), the histological type of large cell lymphoma and the radiation therapy [1,4,8-13].

Young age at diagnosis of the first cancer appears as a risk factor of SPC. In the NCI study, the risk of occurrence of an SPC is multiplied by 6 for patients with a first cancer diagnosed before the age of 18 years. It is multiplied by 2 to 3 for a first cancer diagnosed between 18 and 39 years, and 1.2 to 1.6 between 40 and 59 years [13].

According to a Danish study, the relative risk of second gastric cancer is 16 for patients aged between 45 and 59 years [5]. Our patient was treated for gastric lymphoma at the age of 38 years.

This risk is increased by combination therapy including chemotherapy and radiation therapy [1,3,8]. Chemotherapy is not known to induce solid tumors, but can potentiate the effect of other treatments [8,14]. In a study of about 139 patients treated for gastric lymphoma, the authors found that CHOP type chemotherapy is associated with a higher risk of second gastric cancer (p=0.009) [13]. Further, it is possible that alkylating agents exert a mutagenic and carcinogenic effect [1,3,7,14].

Helicobacter pylori is recognized as a carcinogen and is involved in the development of both gastric lymphoma and adenocarcinoma in 70% of cases [1,6,7,12]. It causes chronic inflammation, cytokines and nitrogenous production who can do cell damage and mutagenesis, causing gastritis, atrophy and metaplasia [1,4,12]. In a literature review, among the 10 patients who had a second gastric cancer after treatment of gastric lymphoma, 9 had an infection with HBP [1]. Our patient had no infection with HBP.

Table 1 summarizes the cases of gastric SPC occurred after gastric

Table 1 Literature cases of second gastric cancers after treatment of gastric lymphoma.

Series	Number of cases Age	First cancer	Treatment	Time limit (months)	Histologic Type de SPC	Treatment
Mc Neer G et al. [6]	1 case F 27 years	Reticulolymphoma	Partial Gastrectomy	78	Adenocarcinoma	Total Gastrectomy
Ettinger DS et al. [21]	1 case M 55 years	Lymphosarcoma	Partial Gastrectomy-RT 26 Gy	256	Adenocarcinoma	Palliative care
Baron BW et al. [22]	4 cases 3M 1 F 24–60 years	DLBCL	RT ABD 31, 5 Gy-Partial Gastrectomy+RT 26 Gy-partial Gastrectomy+CT	48-180	Adenocarcinoma	Partial Gastrectomy-Total Gastrectomy
Copie-Bergman C et al. [14]	4 cases 3 M 1 F 40-65 years	MALT	HBP Eradication - CT	30-204	Intestinal Carcinome	Total Gastrectomy
Seo et al. [4]	1 case M 52 years	MALT	CT:6 cures RT stomach 39.6 Gy	40	Signet ring carcinoma	Partial Gastrectomy
Naoki A et al. [8]	1 case F 58 years	MALT	HBP Eradication -RT stomach 30 Gy	48	Signet ring carcinoma	Endoscopic Resection
Inaba K et al. [13]	10 cas 6 M, 4 F 36- 73 years	DLBCL	CT (3-8 cures) RT stomach 40 Gy	79-90.8	Adenocarcinoma Well differentiated: 4 Moderately differentiated: 1 Poorly differentiated: 1 Signet ring carcinoma: 4	Endoscopic Resection: 6 Gastrectomy: 4

SPC: Second Primary Cancer; F: Female; M: Male; DLBCL: Diffuse Large B-Cell Lymphoma; MALT: MALT Lymphoma; RT: Radiotherapy; ABD: Abdominal; CT: Chemotherapy

lymphoma treatment. Among these cases there have been 14 cases of large B-cell lymphoma, 6 cases of MALT lymphoma, one case of reticulolymphoma and a case of lymphosarcoma. The age at diagnosis of the first cancer ranged from 24 to 73 years. There was a male predominance. Treatment modalities were very different, but some patients had not received chemotherapy or radiotherapy. The 14 cases of B-cell lymphoma, large cell had a combination of chemotherapy and radiotherapy as our patient.

Several cases of second gastric primitive malignant neoplasm after radiotherapy, have been described in the literature [8-11]. It is still not clear the risk of radio-induced cancer because epidemiological uncertainties, unknown biological mechanisms and others co-factors of carcinogenesis [10]. In adults the probability of occurrence of second primary cancer "caused by irradiation" is close to 1 to 2% [9,11].

This risk increases with the delivered dose [15-17]. At doses between 15 and 40 Gy, the highest RR is observed [9]. In adults, the majority of second primary cancers occur near the "target volume" (tissues or organs receives about 50% of the prescribed dose), at a distance not exceeding five cm beyond the limits of beams or in a region receiving doses between 20 and 30 Gy. The risk of cancer of a tissue exposed to radiation varies from one organ to another. In adults, lung, stomach, hematopoietic marrow appeared to be particularly at risk [6,10]. At the same dose, the RR increases with the volume of tissue or irradiated organ. For the same dose to an organ RR is less if part of the body is protected [9,11]. When a second primary cancer appears in the irradiated area, it is difficult to confirm its «radio-induced» origin" [18,19]. A tumor is considered as radiation-induced if it is within the irradiated volume with a different histology and is displayed in a period of more than 5 years after irradiation [18,19].

The occurrence period of second gastric cancer after treatment of gastric lymphoma is often long [19]. After radiotherapy for large B-cell lymphoma **(Table 1)** second gastric cancer occurs after a period of 4 to 15 years [13,20-22]. This period was 11 years in our case. However this period was only 3 to 4 years for type MALT lymphomas [4,8,14].

The histological type of "gastric radiation-induced cancers," reported in the literature is often an adenocarcinoma or signet ring cell carcinoma **(Table 1).**

In our case, it is very likely to be radiation-induced gastric cancer given the time of occurrence of this cancer, in irradiated zone and its histological type.

The treatment of these second gastric cancers is based on surgery and chemotherapy. Surgery should be offered to all operable patients [1]. Chemotherapy is proposed for metastatic patients or after surgery for patients with bad prognostic factors [1,20].

Conclusion

Second primary cancer after treatment of gastric lymphoma is rare. According to the literature, they are observed in male treated in young age. They appear after several years. They are often adenocarcinoma type or signet ring carcinoma. Some of them can be considered as radiation-induced cancers. Their treatment is based mainly on surgery and chemotherapy.

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