Conference Paper

Non-Hodgkin Lymphoma Secondary to Cancer Chemotherapy in a Patient with Small Cell Carcinoma of the Pancreas

Brian Wasita[1], Hanggoro Tri Rinonce[2], Ery Kus Dwianingsih[2], Afif Rahman[3], and Ahmad Ghozali[2]

[1]Anatomical Pathology Department, Faculty of Medicine, Universitas Sebelas Maret, Indonesia
[2]Anatomical Pathology Department, Faculty of Medicine, Universitas Gadjah Mada, Indonesia
[3]Radiology Department, Faculty of Medicine, Universitas Gadjah Mada, Indonesia

Abstract

Increased survival seen in patients with solid cancers achieved through aggressive treatment has transformed the prognosis and the complications of the therapy. The carcinogenic effect of the therapeutical agents has given leads to an increased incidence of second malignancies. This case report describes the rare metachronous association of two malignancies and to discuss the etiological links. A 51-year-old man presented with enlargement of right axilla and mesentery lymph nodes. The patient had a history of small cell carcinoma at the head of the pancreas and was treated with chemotherapy cisplatin and gemcitabine for 12 cycles two years prior. Biopsies were then performed. Diagnosis of Non-Hodgkin Lymphoma (NHL) follicular (nodular) type was decided from microscopic and immunohistochemistry results. We discussed that secondary NHL due to chemotherapy for solid cancer is rare. Testicular cancer, ovarian cancer, and breast cancer are the common primary tumors. The primary tumor from a small cell carcinoma of the pancreas (SCCP) is sporadic. The risk of secondary lymphoma increases after the first five years of completion of chemotherapy or radiotherapy and persists for more than three decades. In conclusion, this case reinforces the need for long-term follow-up of all patients exposed to chemotherapy for the treatment of pancreatic cancer.

Keywords: Secondary NHL, chemotherapy, small cell carcinoma of the pancreas

Corresponding Author:
Brian Wasita
brianwasita@yahoo.com

Received: 23 February 2019
Accepted: 6 March 2019
Published: 25 March 2019

Publishing services provided by Knowledge E

Selection and Peer-review under the responsibility of the ICO-HELICS Conference Committee.

1. Introduction

Recently, patients with solid cancers had an increased survival rate due to aggressive chemo-radiation therapy. Despite favourable survival, the carcinogenic effect of therapeutic agents used in chemo-radiation therapy can lead to a relatively increased incidence of secondary malignancies including secondary Non-Hodgkin Lymphomas (NHL) [1]. This case report describes the rare metachronous association of a rare small cell carcinoma of pancreas and NHL and to discuss the etiological links.

2. Case Presentation

A 51-year-old man was admitted for masses in the right axilla and intra-abdominal area. Biopsy for the mass in the right axilla and laparotomy biopsy for the masses in the mesentery area were then performed. Macroscopic examination of the masses revealed one mass from the right axilla area with a size of 0.9 cm in diameter and two masses from mesentery area with a size of 0.9 and 1.5 cm in diameter. All masses were firm and white-tan color in cut surface. The whole masses were submitted for microscopic examination. Microscopic examination of all masses showed lymph nodes tissue with lymphoid tumor arranged in follicles, which consist of centrocyte and centroblast, with the number of centroblasts of >15/HPF (Figure 1). Diagnosis of Non-Hodgkin Lymphoma of follicular type grade 3 was suspected, and immunohistochemical stains for CD3, CD20, and BCl-2 were suggested to confirm the diagnosis.

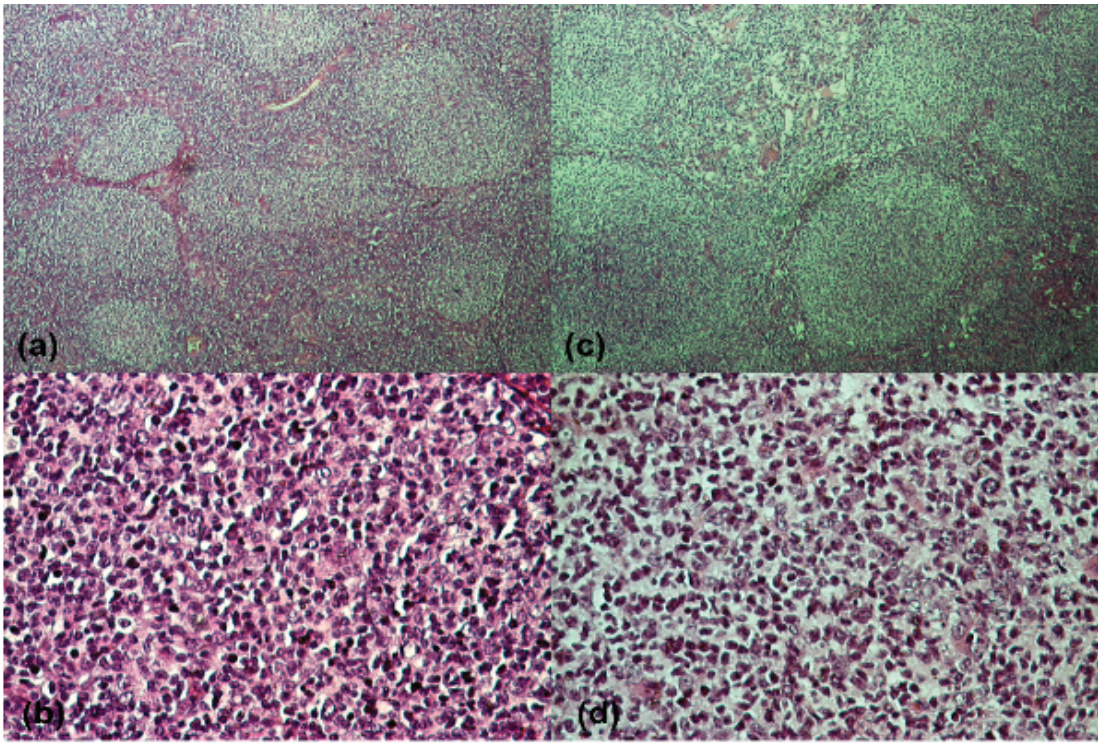

Figure 1: Representative Haematoxylin & Eosin staining showed features of Non-Hodgkin Lymphoma follicular type grade 3. Right axillary lymph node (a) and (b). Mesentery lymph nodes (c) and (d). (a) and (c): 40 x original magnification; (b) and (d): 400x original magnification.

Immunohistochemical stains were performed on the paraffin-embedded sections using a Labelled-Streptavidin Biotin (LSAB) method. CD3 antibody (1:100, Biocare Medical, Pike Lane Concord, USA), CD 20 antibody (1:100, Diagnostic biosystem, California, USA) and BCl-2 antibody (1:100, Abcam, Cambridge, USA) were used. CD3 stain showed positive staining on lymphoid cells outside the tumor (Figure 2[a] and 2[b]). CD20 and

BCl-2 stains showed strong positive staining in all tumor cells (Figure 2C-F). Thus the diagnosis of Non-Hodgkin Lymphoma follicular type grade 3 was decided. The patient received chemotherapy with a regimen of RCHOP (Rituximab, Cyclophosphamide, Doxorubicin Hydrochloride, Vincristine Sulphate, and Prednisone) for five cycles until August 2014.

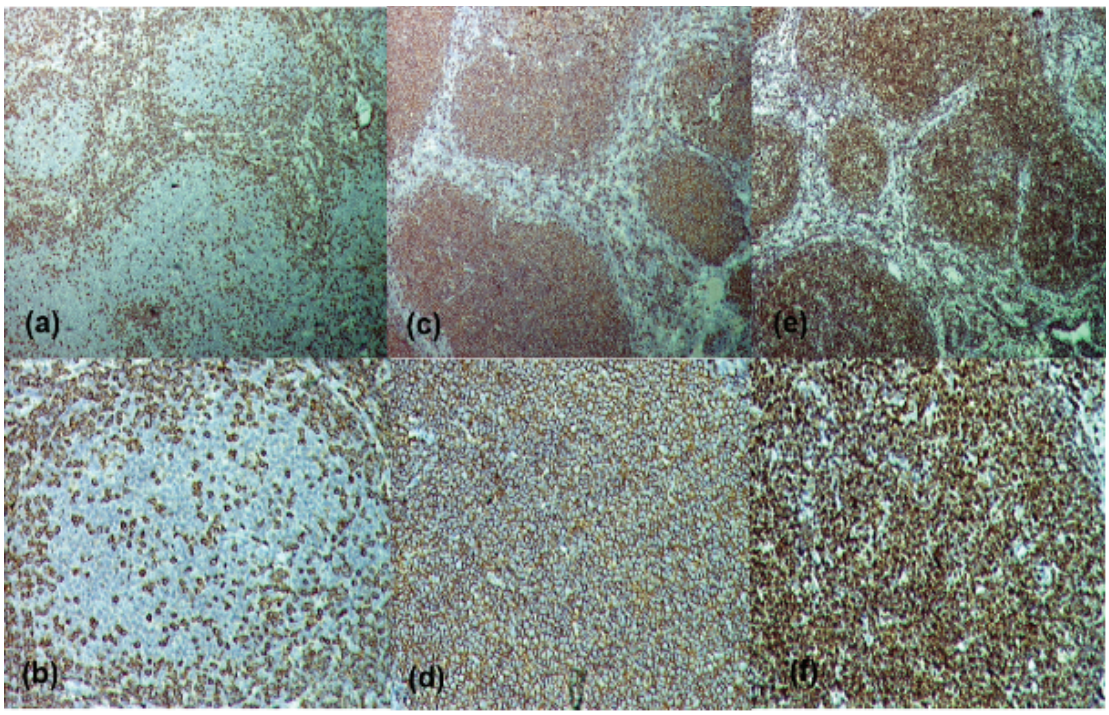

Figure 2: Immunohistochemical stains of a representative paraffin-embedded section. CD3 showed positive cytoplasmic staining on lymphoid cells outside the tumor (a) and (b). CD20 (c) and (d) and BCl-2 (e) and (f) showed strong cytoplasmic positive staining in all tumor cells. (a), (c), and (e): 40x original magnification; (b), (d) and (f): 400x original magnification.

The patient was diagnosed with small cell carcinoma of the pancreatic (SCCP) head two years prior. In April 2012, the patient was admitted with shortness of breath. Chest x-ray showed bilateral pleural effusion with bilateral hilar lymphadenopathy. The pleural puncture was performed, and pleural fluid was sent for cytological examination with the result of inflammation with reactive mesothelial. He has repeated episodes of pleural effusion with cytological examination results of chronic inflammation. Chest x-ray showed no evidence of primary lung cancer and metastasizes Abdominal CT scan was performed and revealed an iso-density well-defined mass at the pancreatic head with a diameter of 2 cm. Laboratory examination showed the elevation of CA 19-9 serum level in two consecutive examinations. One month later, he developed a pleural effusion. The pleural puncture was performed, and cytological examination from another laboratory showed malignant cells with undetermined type with differential diagnosis of small cell neuroendocrine tumor probably metastasis from the pancreas. He was diagnosed as

small cell carcinoma of the pancreatic head and subsequently underwent chemotherapy with a regimen of gemcitabine and carboplatin for six cycles and then change with gemcitabine and oxaliplatin for six cycles. Whole-body PET-CT scan at another hospital taken nine months after initial diagnosis showed multiple lymphadenopathies which were suspected as nodal metastasis and osteolytic metastasis lesions on T2, T9, and L3 vertebrae, right next costume also compression fracture on T9 vertebrae.

3. Discussion

The incidence of secondary Non-Hodgkin lymphomas in patients treated for cancer is less common which account for 5 to 5.9% of incidence rate and their pathogenesis remains controversial [1, 2] Hodgkin lymphoma, testicular cancer, ovarian cancer, and breast cancer are common primary cancer of secondary NHL [3, 4].

Some hypothesis were proposed regarding the pathogenesis of secondary NHL which include radiation, immunosuppression and cytotoxic drugs [1]. Radiation can cause single-and double-strand DNA breaks which increased the chances of aberrant genetic rearrangements [1]. Immunosuppression increases the risk of developing the post-transplant lymphoproliferative disease, hence considering to be the cause of NHL [1]. Cytotoxic drugs are implicated in the pathogenesis of secondary NHL because both alkylating agents and topoisomerase II inhibitors generate double-strand breaks (DSB) of DNA which catalytic processes involved in the repair of DSB that are prone to error and misrepair and chromatid exchange. This could lead to malignant transformation [1, 5]. Secondary NHL from SCCP is extremely rare, in our case chemotherapy using carboplatin and oxaliplatin which belong to platinum-containing anti-cancer drugs have a mechanism like alkylating agents, hence have a potency to induce malignant transformation. Risk of secondary lymphoma increases after the first five years of completion of chemotherapy or radiation therapy and persists for more than three decades [1]. In our case, the patient developed secondary NHL six months after completion of chemotherapy, which was considered faster than the predicted time.

Primary pancreatic small cell carcinoma (SCCP) is a rare cancer, with only a few cases reported in the literature with the incidence rate of only 1% [6, 7]. Pancreatic SCC is now classified as a high-grade neuroendocrine carcinoma [8]. Diagnosis usually decided based on clinical features, abdominal CT scan, elevated serum level of Neuron-Specific Enolase (NSE) and pro-gastrin-releasing peptide (ProGRP), histopathological examination and immunohistochemical staining using NSE and chromogranin A [6, 9]. However, Sakamoto [10] diagnosed four cases of SCCP based on cytological examination

with endoscopic ultrasonography-guided fine needle aspiration (EUS-FNA). In our case, SCCP was diagnosed based on abdominal CT scan, an elevated serum level of CA 19-9 and cytological examination of pleural effusion.

SCCP usually has been metastasized at the time of initial diagnosis and the most frequent sites of metastasis are the peripancreatic lymph nodes (62%), the liver (38%), the lungs (14%), the bone marrow (14%), the colon (10%), the bone (10%), and the adrenal gland (10%); rarer sites included the spleen, gallbladder, kidney, skin, and brain [6]. In our case, the SCCP had been metastasized into the pleura, the lymph nodes, and the bone (costume and vertebrae).

Standard treatment for SCCP has not been established yet due to the rarity of the disease. Surgical therapy remains the standard treatment for well-differentiated neuroendocrine tumors. However, most patients with pancreatic SCC did not undergo surgical therapy as in our case because the benefit of surgery for high-grade neuroendocrine carcinomas has not been established [9]. Thus, combined surgery with adjuvant chemoradiation therapy might improve the prognosis of SCCP [6]. cisplatin-based chemotherapy has been the mainstay of treatment for most histologically similar extrapulmonary small-cell cancers [11], the combination of cisplatin/carboplatin and etoposide is most frequently prescribed in SCCP, therefore a potency to induce malignant transformation is persisting.

Prognosis of SCC is considered poor with the median survival was 20 months. However, some patients survived for more than five years [9]. Our patient survives for 29 months due to aggressive chemotherapy using gemcitabine and carboplatin or oxaliplatin which provide local tumor control.

In conclusion, therapeutic agents used in the therapy of primary cancers causing double-strand breaks of DNA may be implicated as causal factors in the etiology of secondary NHL. This case reinforces the need for long-term follow-up of all patients exposed to chemotherapy in the treatment of pancreatic cancer.

References

[1] Krishnan B, Morgan G J 2007 *Epidemiol.Biomarkers. Prev* **16**(3) 377-80

[2] Rosner F, Grunwald H W 1983 *Arch. Intern.Med.* **143** 2335-9

[3] Hooning M J, Aleman B M, van Rosmalen A J, Kuenen M A, Klijn J G, van Leeuwen FE 2006 *Int. J. Radiat. Oncol. Biol. Phys* **64** 1081-91

[4] Kaldor J M, Day N E, Band P, Choi NW, Clarke E A, Coleman M P, Hakama M, Koch M, Langmark F, Neal F E 1987 *Int. J. Cancer.* **39** 571 – 85

[5] Pedersen-Bjergaard J, Pedersen M, Roulston D, Philip P 1995 *Blood* **86** 3542-52

[6] Wang D, Rong Y, Wu W, Jin D 2012 *World. J. Surg. Oncol.* **10** 32

[7] Reyes CV, Wang T 1981 *Cancer* **47**(10) 2500-02

[8] Kim JY, Hong SM 2016 *Arch. Pathol. Lab. Med* **140**(5) 437-48

[9] Winter J M, Narang A K, Mansfield A S, Herman J M, Cameron J L, Laheru D, Eckhauser F E, Olson M T, Hruban R H, Miller R C, Andersen D K 2011 *Rare Tumors* **3**(1) e5

[10] Sakamoto H, Kitano M, Komaki T, Noda K, Chikugo T, Kudo M 2009 *J. Gastroenterol.* **44(5)**

432-8

[11] Ugwu J K, Nwanyanwu C, Shelke A R 2017 *Case Rep. Oncol.* **10(**2) 720-5