



Case Report

Solid tumors after chronic lymphocytic leukemia patients: Report of six cases and review of the literature

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Abstract

Introduction:

Malignancies have been reported to occur with increased frequency in chronic lymphocytic Leukemia (CLL) patients. The aim of this study was to describe which second malignancies occur in patients with CLL, whether these malignancies are related to CLL, its treatment, or both. We also attempt to study factors predicting the development of other malignancies.

Patients and methods

Between 1995 and 2009, six cases of CLL associated with solid tumor were diagnosed in Hematology Department of Military Hospital of Tunis. The diagnosis of CLL was made by immunophenotyping of peripheral blood circulating B cells, and the diagnosis of solid tumors was made by biopsy with anatomopathological exam and immunohistochemical study.

Introduction

Malignancies have been reported to occur with increased frequency in chronic lymphocytic Leukemia (CLL) patients. Several studies have reported that site-specific excesses of second cancer may exist among patients with CLL^(1,2). Patterns of subsequent neoplasms in these individuals may provide insight into etiologic factors associated with both malignancies.

Results

The mean age of patients was 71 years. Five patients were male. The CLL was classified Stage A in one case, Stage B in three cases and Stage C in two cases. Two patients had abnormal karyotype. Three patients have not received specific treatment for their CLL. Solid tumors were represented by skin cancer in three cases, lung cancer in two cases and breast cancer in one case. The median time between diagnosis of CLL and that of solid tumor was 53 months.

Conclusion

Patients with CLL have an increased risk of developing a second cancer. Awareness of risk factors could permit early detection.

Keywords

tumor, lymphocytic, leukemia, association

In the present study, we try to describe which second malignancies occur in patients with CLL, whether these malignancies are related to CLL, its treatment, or both. We also attempt to study factors predicting the development of other malignancies.

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Reported cases

Case No. 1

Mr. A.M, 76 years old, with history of hypertension and 30 pack–year smoking, had been followed up since 1995 for a CLL initially classified stage A. Three years after diagnosis, a biological progression had been noticed (anemia and thrombocytopenia). The disease was reclassified stage C and the patient was treated by mono chemotherapy based on cyclophosphamide, with clinical and biological response. In 2007, 12 years after the diagnosis of CLL, the patient consulted after the appearance of a skin lesion on his back. Skin biopsy had confirmed the diagnosis of squamous cell carcinoma. The patient had a surgical resection of the tumor.

Case No. 2

Mr. CA, 62 years old, without medical history, had been followed up since 2006 for CLL, classified stage B. Deletion of 13q14 was detected in the karyotype. The patient received no specific treatment with regular clinical and biological monitoring. In 2011, 5 years after diagnosis of CLL, the patient had an ulcerative skin lesion on his face. Skin biopsy had

confirmed the diagnosis of basal cell carcinoma. The patient had a surgical resection of the tumor.

Case No. 3

Mr. HM, 78 years old, with history of hypertension and 50 pack–year smoking, had been followed since 2006 for CLL, classified stage B. The patient received no specific treatment with regular clinical and biological monitoring. In 2011, the patient consulted after progressive onset of dyspnea and chest pain. The radiological assessment (chest X–ray, CT scan) showed lung opacity. The CT guided biopsy had confirmed the diagnosis of pulmonary adenocarcinoma. The disease was classified stage IV and the patient received palliative chemotherapy. The death occurred eight months after diagnosis.

Case No. 4

Mr. A.P, 82 years old, had been followed since 2010 for CLL, classified stage C. He was treated with single–agent chemotherapy based on chlorambucil, with clinical and biological stability. In 2012, two years after, the clinical examination revealed a pigmented skin lesion on the anterior surface of the right leg, the biopsy had confirmed the diagnosis of

Case number	Gender	Age	Date of diagnosis of CLL	CLL stage	Treatment of CLL	Date of diagnosis of solid tumor	Histological type	Solid tumor stage	Treatment of solid tumor
1	male	76	1995	Initially A then reclassified C	cyclophosphamide	2007	Squamous cell carcinoma of the skin	localized	Surgical resection
2	male	62	2006	B	–	2011	Basal cell carcinoma of the skin	localised	Surgical resection
3	male	78	2006	B	–	2011	Lung adenocarcinoma	IV	Palliative chemotherapy
4	male	82	2010	C	chlorambucil	2012	Melanoma	I	Surgical resection
5	male	76	2010	C	chlorambucil	2011	Lung adenocarcinoma	IV	Palliative chemotherapy
6	female	52	2009	B	–	2010	Breast ductal carcinoma	T2N0M0	Patey and adjuvant CT and RT

Table 1: Clinical findings on the six cases

CLL: chronic lymphocytic leukemia; CT: chemotherapy; RT: radiotherapy

melanoma. The patient underwent surgical resection with lymph node dissection.

Case No. 5

Mr. S.I, 76 years old, with history of 40 pack–year smoking, had been followed since 2010 for CLL stage C. He was treated with single–agent chemotherapy based on chlorambucil, with clinical and biological stability. In 2011, the patient consulted after progressive onset of dyspnea, persistent cough and hemoptysis. The radiological assessment (chest X–ray, CT scan) showed the presence of suspicious lung opacity. The CT guided biopsy had confirmed the diagnosis of pulmonary adenocarcinoma. The disease was classified stage IV and the patient received palliative chemotherapy. The death occurred six months after diagnosis.

Case No. 6

Mrs. J.S, 52 years old, had been followed since 2009 for CLL, classified stage B. Deletion of 13q14 was detected in the karyotype. The patient received no specific treatment with regular clinical and biological monitoring. In 2010, she discovered a lump in her left breast. The mammography had classified the lesion as ACR5. The ultra–sound guided biopsy confirmed the diagnosis of invasive ductal carcinoma. A left Patey mastectomy was performed followed by adjuvant radiotherapy and chemotherapy, and then the patient received hormone therapy.

The table 1 below summarizes the clinical findings on the six cases

Discussion

CLL is the most frequent leukemia in Western countries. Genetic factors seem to play a role in the pathogenesis of the disease. Karyotype abnormalities are found in 50 to 80% of cases. The 13q14 deletion is the most frequent. The 11q22–23 deletions, trisomy 12, and p53 mutation or deletion on chromosome 17 are associated with more aggressive disease ⁽³⁾.

Reports suggesting an increased incidence of so–called solid tumors in patients with CLL have appeared for at least 30 years. In the United States, an early retrospective analysis in 1975 by Manusow and Weinerman about 102 patients with CLL suggested that the incidence of second cancers was elevated

in comparison to the general population. The risk for developing all cancer in CLL patients was found to be 3–fold that for the age– and sex–matched population, 8–fold for skin cancers, and 2–fold for all cancers ⁽¹⁾.

Greene et. al. noted that 234 among 4869 CLL patients had developed a second malignancy compared with 204.9 expected. The risk was significantly elevated for malignant melanoma, soft tissue sarcomas, and lung cancer ⁽²⁾.

Mellemsgaard et. al. (7391 CLL patients) found an increased overall risk for cancer in CLL patients. The standardized incidence ratios (ratio between the observed and the expected numbers) were 2.0 for men and 1.2 for women ⁽⁴⁾.

More recently the National Cancer Institute (NCI) study initially reported by Greene et al. has been expanded and updated by Hisada et. al. ⁽⁵⁾. This study quantified the risk of second cancers among 16,367 patients with CLL in the population–based Surveillance, Epidemiology and End Results Program. Overall, the observed/expected ratio (O/E) was 1.20 (95% confidence interval (CI), 1.15–1.26). Significant excess was found for Kaposi’s sarcoma, malignant melanoma, laryngeal carcinoma, and lung cancer.

An American retrospective study conducted from 1985 to 2005 by Tsimberidou et al. including 2028 patients with CLL, found that the risk of second cancer was 2.2 times higher than the expected risk. The major types of cancer were as follows: skin carcinomas, prostate, breast, melanoma and gastrointestinal ⁽⁶⁾.

Another retrospective study from Italy, by Mauro et al. observed 1011 CLL patients (204 patients (20%) ≤ 55 years old and 807 patients (80%) older than 55 years) over a period of 10 years. Both groups showed an elevated rate of second primary cancers (8.3% vs 10.7%) ⁽⁷⁾.

Over the last decades, it became clear that CLL is characterized by abnormal in both cell and humoral–mediated immunity. In fact, Greene et. al. support immunologic deficiency in CLL to be involved in the excess cancer risk because a similar array of non–hematologic tumors is seen after immunosuppressive therapy in renal transplant recipients ⁽²⁾.

Besides, hypogammaglobulinemia represents a widespread and clinically important immune defect. Its frequency and severity progress as the duration of CLL advances ⁽⁸⁾. Commonly, all 3 immunoglobulin classes (IgG, IgA, and IgM) are decreased, but in some patients only 1 or 2 sub-class may be low. Occurrence of malignant tumors was demonstrated in patients having a background of humoral immunodeficiency, such as common variable immunodeficiency, which was associated with lymphomas and gastric carcinoma ⁽⁹⁾.

A complex array of abnormal immunoregulatory T-cell functions was demonstrated by Perri and Kay ⁽¹⁰⁾ in early-stage CLL. Those include a prominent T-helper dysfunction and a more variable excessive T-suppressor activity. Development of neoplasm has been linked to abnormalities in T-cell function. One example is ataxia-telangiectasia, which is characterized by mutations in ATM (ataxia-telangiectasia mutated), resulting in deficient T-cell development and a predisposition to T-cell leukemia and other lymphoid neoplasms ^(11,12). Moreover, T-cell abnormalities similar to those seen in CLL are encountered in HIV disease and are associated with the development of Kaposi's sarcoma, non-Hodgkin's lymphoma, and cervical cancer ⁽¹³⁾.

Some investigators argue that purine analogs have direct carcinogenic effects or increase the risk of Richter's transformation in patients with CLL ⁽¹⁴⁾. However, the NCI study updated by Hisada et. al. demonstrated that second cancer risks were similar in treated or untreated patients ⁽⁵⁾. Furthermore, a retrospective analysis of patients with CLL treated with cladribine based regimens and/or alkylating agents based regimens in eight hematological departments in Poland performed by Robak et. al. found that cladribine does not increase the risk of secondary malignancies except for lung cancers in CLL patients ⁽¹⁵⁾.

Moreover, Greene et. al. thought that therapy of CLL was not the cause of the second tumor because the excess risk persisted throughout the period of follow-up ⁽²⁾.

In conclusion, there is no compelling evidence that either purine nucleoside analogs or alkylating agents are associated with an increased incidence of second malignancies in patients with CLL. However,

new powered studies are necessary to validate these conclusions.

Concerning the treatment with monoclonal antibodies, as a chief Rituximab which is an active agent targeting the CD20 antigen present in surface of neoplastic B lymphocytes, studies have showed that Rituximab interfered with the humoral response as well as with the memory response ⁽¹⁶⁾. However the occurrence of second cancers in this context is still unknown ⁽¹⁷⁾.

Conclusion

In conclusion, our study emphasizes that other malignancies frequently coexist with CLL. An association between CLL treatment and the development of other cancers is not evident.

Further investigation of genetic features that predispose patients with CLL to develop other malignant solid tumors is needed. Even with our current imperfect understanding of the predisposition for second cancers, awareness of the risk could permit early detection of these malignancies.

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