Spindle Cell Sarcoma: A Case of Non-AIDS-defining Cancer

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Abstract

Since the advent of HAART, patients with HIV infection have seen a significant improvement in their morbidity, mortality, and life expectancy. The incidence of AIDS-defining illnesses, including AIDS-defining malignancies, has been on the decline. However, deaths due to non-AIDS-defining illnesses have been on the rise. These so-called non-AIDS-defining cancers (NADCs) include cancers of the lung, liver, kidney, anus, head and neck, and skin, as well as Hodgkin's lymphoma. Spindle cell sarcoma is the one of NADCs. The development of NADCs appears to be multifactorial. Risk factors include immunosuppressive effects of the HIV, higher rates of oncogenic viral coinfections and traditional cancer risk factors. A male patient who was HIV-infected with a complaint of ulcerated growth at left maxilla that challenges to his practitioner for diagnosis was presented in this paper. New strategies for screening, prevention and treatment of NADCs need to be developed to reverse these epidemiologic trends and improve the survival of HIV-infected patients.

Key words: AIDS-defining cancers, Non-AIDS-defining cancers, Spindle cell sarcoma, Epithelial membrane antigen, Vimentin.

Introduction

Since the advent of HAART, patients with HIV infection have seen a significant improvement in their morbidity, mortality, and life expectancy. The incidence of AIDS-defining illnesses, including AIDS-defining malignancies, has been on the decline. However, deaths due to non-AIDS-defining illnesses have been on the rise. These so-called non-AIDS-defining cancers (NADCs) include cancers of the lung, liver, kidney, anus, head and neck, and skin, as well as Hodgkin's lymphoma. It is poorly understood why this higher rate of NADCs is occurring. The key challenge facing oncologists is how to administer chemotherapy effectively and safely to patients on antiretroviral therapy. The challenge to clinicians caring for HIV-infected patients is to develop and implement effective means to screen, treat, and prevent NADCs in the future (Deeken *et al*., 2012).

Sarcomas comprise a heterogeneous and biologically diverse group of malignant neoplasms having as a common denominator their origin from mesenchymal cells. Head and neck sarcomas account for 4 to less than 20% of total body sarcomas depending on the criteria, such as age of patients (pediatric vs adult population), type of sarcomas (soft-tissue vs bony sarcomas) and site of location. Sarcomas display a diverse array of histology and a wide spectrum of clinical behavior, ranging from relatively slow growing lesions to aggressive locally and regionally destructive tumors with the potential for systemic metastases. Survival rates for head and neck sarcomas suggest worse outcomes than for their extremity counterparts. Lymph node metastasis only occurs in 3-10% of sarcomas of the head and neck. An improvement in local disease control has recently been suggested with the combined use of surgery and radiotherapy. Conflicting results have been reported on the benefit from the use of chemotherapy as an adjuvant or neoadjuvant regimen, especially for high-grade sarcomas in long-term survival or local disease control. Encouraging results have recently been reported with the use of molecular targeted therapies with tyrosine kinase inhibitors and antiangiogenetic agents (Rapidis, 2008).

In the days before the term "high-grade undifferentiated pleomorphic sarcoma" came into use, one of the most common sarcoma diagnoses was "malignant fibrous histiocytoma," and before that, in an era before immunohistochemistry, "fibrosarcoma" was used to describe most sarcomas. "Spindle cell" is a descriptive phrase that denotes the cellular shape of many of the sarcomas encountered in the adult population. As a result, they are usually treated differently from small round cell sarcomas, and have different biological characteristics than those tumors and sarcomas with epithelioid morphology. As a very broad generalization, sarcomas with a spindle cell microscopic morphology occur in adults and are treated primarily with surgery and often adjuvant or neoadjuvant radiation as primary therapy. In comparison to small round cell sarcomas such as Ewing sarcoma, the use of adjuvant chemotherapy

remains controversial, and the sensitivity of these tumors to chemotherapy in the metastatic setting is highly variable (Collini *et al*., 2009).

Case report

A 45-year-aged, HIV-infected male patient came to Oral Medicine Department, University of Dental Medicine, Yangon, with complaint of ulcerated growth at left maxillary region for 7 months. On examination, the lesion was exophytic growth from 34 teeth to 38 teeth, mobility of teeth was grade II mobility and bilateral submandibular lymph nodes were palpable. The case was provisionally diagnosed as malignant growth or lymphoma by Primary care dental surgeon. Incisional biopsy was done by Oral Surgeon and the specimen was sent to Oral Pathology Department. Routine Hematoxylin & Eosin (H&E) staining was done and seen under microscope (Figure. 1).

Microscopic examination of this specimen reveals intact atrophic as well as hyperplastic stratified squamous oral epithelium and underlying tumor portion. Epithelium is hyperparakeratinized stratified squamous with acanthosis, inflammatory exocytosis, cellular and nuclear pleomorphism, hyperchromatism and basal cell degenerations. Underlying tumor portion is composed of spindle-shaped cells showing cellular and nuclear polymorphism, various stages of mitoses and tumor giant cells. Spindle-shaped cells are arranged in storiform pattern. Numerous lymphoplasmocytic infiltrations and PMNLs, as well as macrophages, blood filled capillaries with areas of hemorrhage are observed. Provisional diagnosis was spindle cell carcinoma and spindle cell sarcoma.

To confirm the diagnosis, immunohistochemical (IHC) examination was done with epithelial membrane antigen (EMA) and vimentin. Tumor portions were negative for EMA and positive for vimentin (Figure. 2). Finally, the case was diagnosed as spindle cell sarcoma of left maxilla.

Discussion

EMA is an excellent marker of epithelial differentiation, appears to be highly reliable for discriminating between poorly differentiated carcinomas and malignant lymphomas, and is especially helpful in characterizing small cell anaplastic carcinomas. Epithelial membrane antigen immunoreactivity is well preserved in paraffin sections of routinely processed tissues, facilitating application of this technique in diagnostic surgical pathology (Pinkus and Kurtin, 1985).

Vimentin, a major constituent of the intermediate filament family of proteins, is ubiquitously expressed in normal mesenchymal cells and is known to maintain cellular integrity and provide resistance against stress. Vimentin is overexpressed in various epithelial cancers, including prostate cancer, gastrointestinal tumors, and tumors of the central nervous system, breast cancer, malignant melanoma, and lung cancer. Vimentin's overexpression in cancer correlates well with

accelerated tumor growth, invasion, and poor prognosis; however, the role of vimentin in cancer progression remains obscure. In recent years, vimentin has been recognized as a marker for epithelial-mesenchymal transition (EMT). Although EMT is associated with several tumorigenic events, vimentin's role in the underlying events mediating these processes remains unknown. By virtue of its overexpression in cancer and its association with tumor growth and metastasis, vimentin serves as an attractive potential target for cancer therapy; however, more research would be crucial to evaluate its specific role in cancer. Our recent discovery of a vimentin-binding mini-peptide has generated further impetus for vimentin-targeted tumor-specific therapy. Furthermore, research directed toward elucidating the role of vimentin in various signaling pathways would reveal new approaches for the development of therapeutic agents. This review summarizes the expression and functions of vimentin in various types of cancer and suggests some directions toward future cancer therapy utilizing vimentin as a potential molecular target (Satelli and Li, 2011).

NADCs are contributing significantly to the morbidity and mortality of HIV infection in the era of highly active antiretroviral therapy and the risk of NADCs does not correlate with the degree of immunodeficiency in general (Stebbing *et al*., 2009).

People with HIV with mild immune deficiency prior to AIDS were at increased risk of anal cancer, but this may reflect other risk factors. Other cancers occurred only later in the course of HIV infection. This is reassuring evidence that people with HIV who are only mildly immune deficient may not be at increased risk of non-AIDS-defining cancers, but larger studies with longer periods of follow-up are needed to confirm this (Grulich *et al*., 2002).

Newer targeted therapies are now available to treat cancers which were historically refractory to traditional cytotoxic chemotherapy. Highly active antiretroviral therapy agents are notorious for causing drug-drug interactions. The co-administration of targeted chemotherapies with highly active antiretroviral therapy could well impede the efficacy or increase the toxicity of these targeted therapies. Unfortunately little is known about possible drug-drug interactions because HIV patients are typically excluded from clinical trials (Deeken *et al.*, 2009).

HIV appears to be a marker of behavioral or family-related risk factors that affect the incidence of HNC in HIV patients (Engsig *et al*., 2011). Modifiable risk factors, such as smoking and low CD4 counts, were associated with mortality following a diagnosis of NADC (Worm *et al*., 2013).

Conclusion

In conclusion, the incidence of AIDS-defining illnesses, including AIDS-defining malignancies, has been on the decline. However, deaths due to non-AIDS-defining illnesses have been on the rise. These so-called non-AIDS-defining cancers (NADCs) include cancers of the lung, liver, anus,

Hodgkin's lymphoma and Head and Neck cancers. These NADCs are challenging to clinician for diagnosis and their pathological features are diverse. The development of NADCs appears to be multifactorial. Risk factors include immunosuppressive effects of the HIV, higher rates of oncogenic viral coinfections and traditional cancer risk factors. New strategies for screening, prevention and treatment of NADCs need to be developed to reverse these epidemiologic trends and improve the survival of HIV-infected patients.

References

Deeken, J. F., Pantanowitz, L., &Dezube, B. J. (2009). Targeted therapies to treat non-AIDS-defining cancers in patients with HIV on HAART therapy: treatment considerations and research outlook. *Current Opinion in Oncology*, *21*(5), 445–54. http://doi.org/10.1097/CCO.0b013e32832f3e04

Engsig, F. N., Gerstoft, J., Kronborg, G., Larsen, C. S., Pedersen, G., Pedersen, C., &Obel, N. (2011). Head and neck cancer in HIV patients and their parents: a Danish cohort study. *Clinical Epidemiology*, *3*, 217–27. http://doi.org/10.2147/CLEP.S19875

Grulich, A. E., Li, Y., McDonald, A., Correll, P. K., Law, M. G., &Kaldor, J. M. (2002). Rates of non-AIDS-defining cancers in people with HIV infection before and after AIDS diagnosis.*AIDS*, *16*(0269-9370 (Print)), 1155–1161. http://doi.org/10.1097/00002030-200205240-00009

Pinkus, G. S., & Kurtin, P. J. (1985). Epithelial membrane antigen--a diagnostic discriminant in surgical pathology: immunohistochemical profile in epithelial, mesenchymal, and hematopoietic neoplasms using paraffin sections and monoclonal antibodies. *Human Pathology*, *16*, 929–940.

Rapidis, A. D. (2008). Sarcomas of the head and neck in adult patients: current concepts and future perspectives. *Expert Review of Anticancer Therapy*, *8*(8), 1271–97. http://doi.org/10.1586/14737140.8.8.1271

Satelli, A., & Li, S. (2011). Vimentin in cancer and its potential as a molecular target for cancer therapy.*Cellular and Molecular Life Sciences : CMLS*, *68*(18), 3033–46. http://doi.org/10.1007/s00018-011-0735-1

Stebbing, J., Duru, O., & Bower, M. (2009).Non-AIDS-defining cancers.*Current Opinion in Infectious Diseases*, *22*(1), 7–10. http://doi.org/10.1097/QCO.0b013e3283213080

Worm, S. W., Bower, M., Reiss, P., Bonnet, F., Law, M., Fätkenheuer, G., Sabin, C. a. (2013). Non-AIDS defining cancers in the D:A:D Study--time trends and predictors of survival: a cohort study. *BMC Infectious Diseases*, *13*, 471. http://doi.org/10.1186/1471-2334-13-471

Figures

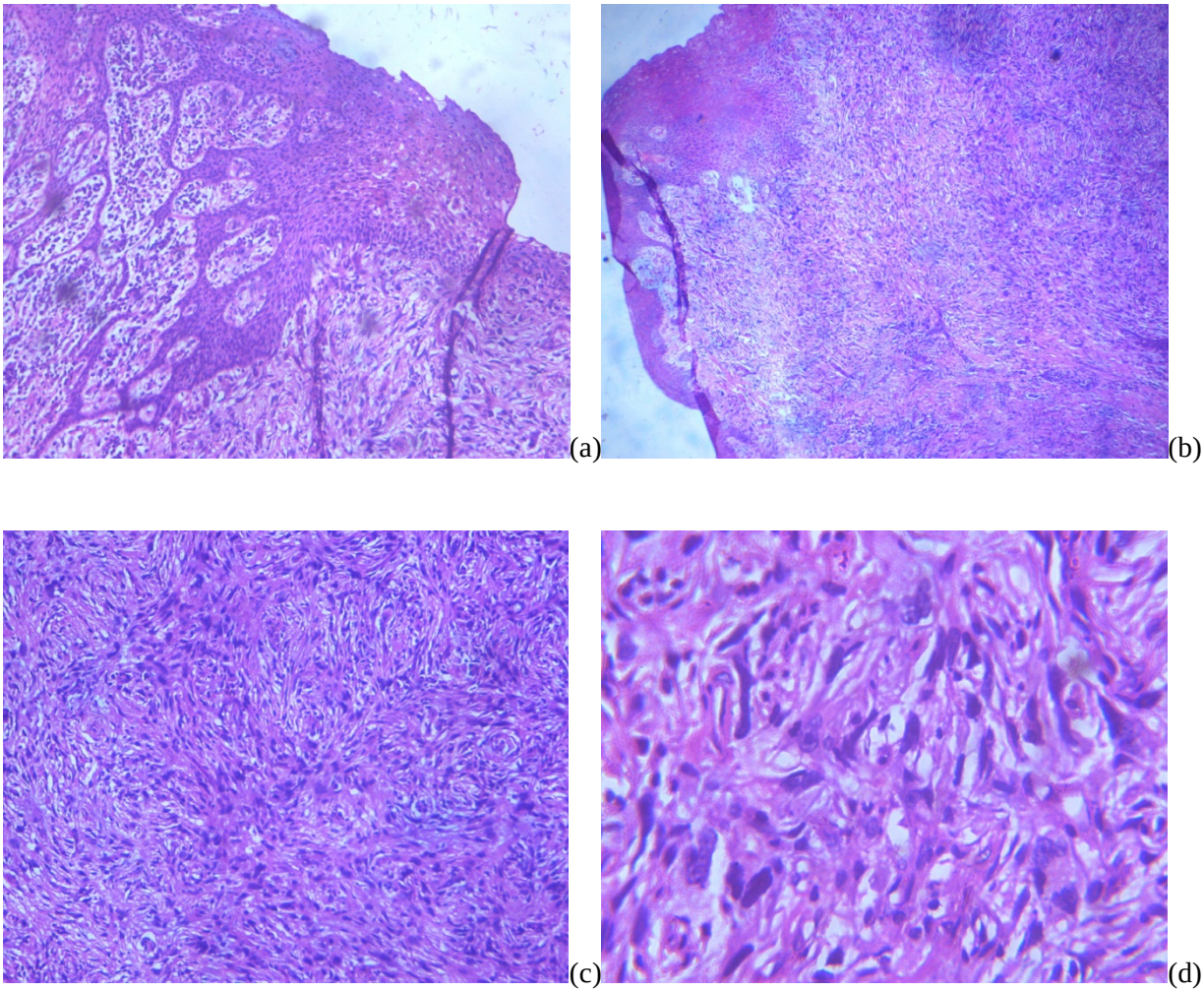


Figure 1.H&E staining of the case. Figure (a) and (b) show atrophic and hyperplastic epithelium and underlying tumor portion (10 x magnifications). Figure (c) reveals that tumor portion is composed of spindle-shaped cells showing cellular and nuclear polymorphism, various stages of mitoses and tumor giant cells. Spindle-shaped cells are arranged in storiform pattern (40 x magnifications) and (d) 200 x magnifications.

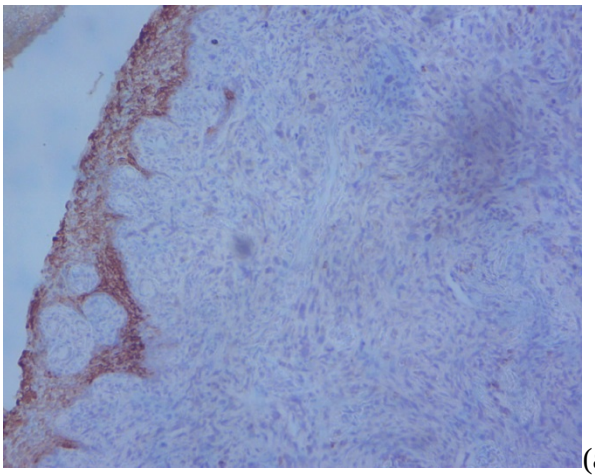
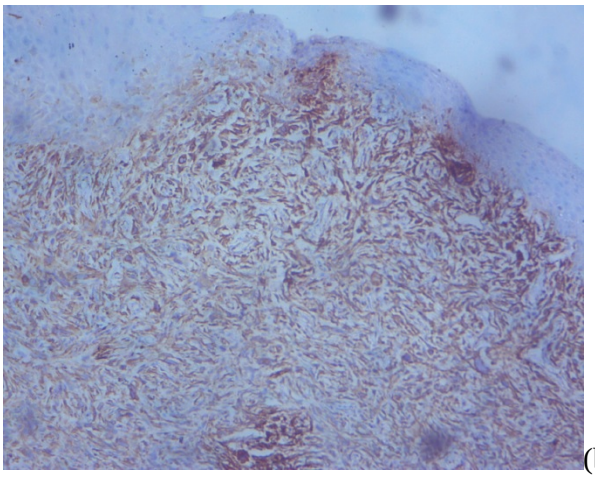

(a)

(b)

Figure 2.IHC staining of the case. (a) EMA is positive in surface epithelium and negative in tumor portion (10 x magnifications). (b) Vimentin is negative in surface epithelium and positive in tumor portion (10 x magnifications).