

A PEER-REVIEWED ARTICLE

Cancer of unknown primary site is on the increase in HIV-infected populations

Marco Ruiz, MD, MPH

Even though the incidence of AIDS-defining cancers has decreased with the use of antiretroviral therapy, non-AIDS-defining cancers have increased in HIV-infected patients as suggested by numerous studies.^{1,2} Among these malignancies, cancer of unknown primary is not a rare occurrence in non-HIV populations.^{3,4,5,6} Unfortunately, there have been no extensive data published about cancer of unknown origin relating to HIV patients, other than some descriptive studies.^{2,7}

Cancer of unknown primary site (CUP) accounts for 0.5% to 10% of all cancers in the general population and represents about 2% of the total prevalence of cancer in the United States.⁴ This entity is characterized by the development of early, uncommon, systemic metastases, with significant resistance to treatment and with poor prognosis.^{4,5,6} These tumors have a unique clinical presentation due to their specific biology.⁸

Multiple attempts to improve diagnosis and identification of the primary source have been reported. Such reports emphasize the use of refined pathologic analysis with immunohistochemistry and molecular genetics, the use of positron emission tomography, breast magnetic resonance imaging, and fiberoptic endoscopy.^{9,10,11} Gene expression profiling when feasible has been found useful in the identification of primary tumors.^{12,13} Autopsy studies have shown that the most common primary sites are lungs, pancreas, hepatobiliary tree, kidneys, genital system, and gastrointestinal tract.¹⁴

Chemotherapy with taxanes and platins has been the mainstay of treatment for this type of cancer. New chemotherapy regimens have also shown benefit in the short term.¹⁵ Angiogenesis is very active and the expression of vascular endothelial growth factor (VEGF) is almost universal in cancers of unknown primary.¹⁶ This new finding has been the basis for new targeted therapies currently under investigation.^{16,17,18}

There are significant questions about the behavior of cancer of unknown primary in HIV-positive patients. Certain issues are still controversial, such as the prevalence in HIV populations, cancer dynamics, mutations, most likely primary sources of cancer, treatment options, influence of antiretroviral therapy in the survival of these patients, and long-term follow-up.

This article will present a case and explore the prevalence of cancer of unknown primary in HIV-infected patients, influence of immunosuppression on cancer behavior, most likely primary sites, and treatment options for this still-unresolved problem.

Clinical Case

A 40-year-old African American female, positive for HIV with CD4 count of 600, was admitted complaining of a large left supra-clavicular mass and generalized fatigue. An initial fine needle aspiration (FNA) of that mass showed potential malignant cells for lymphoma, therefore the patient underwent CT scanning, which showed massive lymphadenopathy compatible with neoplasm involving the cervical, left supra-clavicular, axillary, and superior mediastinal nodes, with displacement of larynx, trachea and

esophagus and left pleural effusion. The patient had an excisional biopsy for further identification that only reported one tumor cell stained focally with keratin and S100 stains suggestive of a tumor of epithelial origin. All tumor cells were negative for all other antibodies. A Port-A-Cath[®] was placed in order to start chemotherapy. Hematology-Oncology was consulted and started a regimen with platins and taxanes as first line of treatment against carcinoma of unknown origin. Bone marrow biopsy, as well as CSF and pleural effusion samples, returned negative for malignancy. After the first course of chemotherapy, the patient developed a catheter infection with coagulase-negative staphylococcus after which she received a course of vancomycin for ten days and removal of the Port-A-Cath. The patient later developed the presence of two hemorrhagic brain metastases. The Oncology team, patient and family decided not to pursue any further interventions. The patient was discharged home and hospice care was arranged.

Incidence and prevalence

Few studies have mentioned the prevalence of cancer of unknown primary site on HIV-infected patients, perhaps due to the lack of precise data. A review on malignancies in HIV-infected patients in Thailand showed a low site incidence.⁷ A more recent review in the United States showed an incidence of 23 per 100,000 person-years.²³

The frequency of non-AIDS-defining cancer is increasing worldwide. Among the possible contributors to the increased prevalence of non-AIDS-defining cancers are greater prevalence of co-infection with viruses that have etiologic roles in cancer and endothelial cell abnormalities including the elaboration of angiogenic factors, which could serve to facilitate tumor growth.²⁵

Studies have shown that among the different types of non-AIDS-defining cancers, it appears that solid tumors and hematologic malignancies might be more prevalent in HIV-infected patients.²³ In an attempt to extrapolate that information into cancers of unknown primary, solid tumors might then be the most common potential “missed primaries.” This is a supposition since there are no studies detailing to the most common potential primary sites.

Biology

There is no consensus as to whether cancer of unknown primary is simply a group of metastatic tumors with unidentified primaries or a distinct entity with specific genetic/phenotypic aberrations that define it as “primary metastatic disease.”⁴ The regression of the primary site is one of the hallmarks of this clinical entity.⁴ It has also been shown that patients with cancer of unknown primary have early metastases; frequently three or more organs are involved, with metastases being commonly localized in unusual sites such as the kidneys, skin, scalp, heart, and distant lymph nodes.⁴

Cancers of unknown primary have chromosomal abnormalities such as aneuploidy, which is seen in 70% of patients and might reflect derangements of chromosomal replication during cell division.⁴ Abnormalities of the short arm of chromosome 1(1p) and of chromosome 12 have also been found.⁴ The presence of isochromosome i (12p) has been related to response to cisplatin-based chemotherapy.⁴

Proteins such as c-Myc, Ras, human epidermal growth factor receptor (HER)-2 are also frequently present in cancer of unknown origin.⁴ Co-expression of HER-2, with epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) or

cyclooxygenase (COX-2), has also been observed in more than half of all cancers of unknown primary.⁴

Expression of p53 has been reported in almost 50% of cases of this type of cancer and also in very advanced cancers.⁴ The metastasis-prone behavior of the cancers of unknown primary is most likely defined by functional deficiency of metastasis-suppressor or tumor-suppressor genes.⁴ A highly active angiogenic profile of cancer of unknown primary has been established.⁴ Universal or frequent expression of key regulators such as VEGF, metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMP-1) has been found. Multigene and tissue protein microarray methodology would potentially help to elucidate the biology of this type of cancer.^{4,12,13,14}

The biology of this entity has not been well studied in HIV-infected patients. It appears that these conditions have an earlier onset and a worse prognosis in HIV-infected patients than in the general cancer population.²⁵ Some studies have also shown that HIV increases susceptibility to such cancers through the direct effects of the virus (genetic instability and increased susceptibility to carcinogens, for instance) and long-term immunosuppression.^{20,21} Assuming that cancer of unknown primary in HIV patients follows the same pattern as non-AIDS-defining malignancies, it would be expected that it would be more aggressive. The role of chromosomal mutations and the expression of certain proteins have not been studied in an HIV environment.

It has also been suggested that neither T cell counts at the time of diagnosis nor T cell count nadir was predictive of non-AIDS-associated malignancies.²⁵ Viral load has also been studied and it appears that its influence is not significant in relation to prevalence of non-AIDS cancers.²⁰ Potential questions might arise in relation to the influence of T cell counts and viral load on the behavior of cancers of unknown primaries in HIV patients.

Pathology

Cancer of unknown primary is classified into four major histo-pathological sub-types: (1) well to moderately differentiated adenocarcinomas (50%), (2) undifferentiated or poorly differentiated adenocarcinomas (30%), (3) squamous cell carcinomas (15%), and (4) undifferentiated neoplasms (5%), including poorly differentiated carcinomas, neuroendocrine tumors, lymphomas, germ cell tumors, melanomas, sarcomas, and embryonal malignancies.^{8,9,15,16} The clinical presentation, diagnostic procedure, treatment, and prognosis vary considerably among the above-mentioned subgroups.⁸

Favorable and unfavorable clinical-pathological entities of cancer of unknown primary have been identified.^{8,17}

Favorable subsets

1. Women with papillary adenocarcinoma of the peritoneal cavity
2. Poorly differentiated carcinoma with midline distribution (extragonadal germ cell syndrome)
3. Poorly differentiated neuroendocrine carcinomas
4. Women with adenocarcinoma involving only axillary lymph nodes
5. Squamous cell carcinoma involving cervical lymph nodes
6. Men with blastic bone metastases and elevated PSA (adenocarcinoma)
7. Isolated inguinal adenopathy (squamous carcinoma)
8. Patients with a single, small, potentially resectable tumor

Unfavorable subsets

1. Adenocarcinoma metastatic to the liver or other organs
2. Non-papillary malignant ascites (adenocarcinoma)
3. Multiple cerebral metastases (adeno or squamous carcinoma)
4. Multiple lung/pleural metastases (adenocarcinoma)
5. Multiple metastatic bone disease (adenocarcinoma)

Scenarios with greatest potential for long-term survival⁹

1. Axillary nodal adenocarcinoma
2. Peritoneal carcinomatosis
3. Unrecognized extragonadal germ cell tumors
4. Squamous cell cancer involving cervical lymph nodes
5. Poorly differentiated neuroendocrine carcinoma

In our case, the patient initially showed a significant development of neck masses and lymphadenopathy. The initial positive stains for keratin and S-100 revealed the possibility of an epithelial-origin tumor (most likely carcinoma). The later development of multiple cerebral metastasis contributed to a more unfavorable subset.

Diagnosis

The diagnostic evaluation of a patient with cancer of unknown primary site consists of establishing the diagnosis of cancer and then searching for the primary site of origin of the tumor.³

Extensive clinical evaluations with pathology review and use of imaging studies have been the mainstay of evaluation of cancer of unknown primary.³ Multiple studies have shown the importance of immuno-histochemistry evaluation for identification of this cancer.¹⁹ The wide use of PET scanning, as well as other nuclear medicine methods such as bone scan and thyroid scintigraphy, have been advocated by numerous authors.^{9,10,11} Endoscopic procedures, when suitable, have also been advocated.^{9,20}

One potential approach to categorizing cancer of unknown primary is to divide it into two groups: carcinomas of unknown primary (adenocarcinoma, squamous cell, poorly differentiated, and neuroendocrine) and poorly differentiated cancer of unknown primary (those that cannot be proven to be carcinoma). This classification would help clinicians to stratify these malignancies and anticipate potential prognoses. More extensive studies might be needed in certain cases when the suspicion for the presence of a malignancy is high in spite of the initial negative workup. It is important to mention that adenocarcinoma of unknown primary remains the one most commonly encountered in medical practice.⁹

The diagnostic methodology for cancers of unknown primary in HIV-infected patients has not been well defined. It is unclear whether HIV-infected patients should have a more aggressive approach in terms of diagnosis workup.

Treatment

Even when the primary tumor remains unknown, curative treatment is possible with radiation therapy, surgery, chemotherapy, or a combined approach in non-HIV-infected

patients. Long term survival has been described.²¹ Chemotherapy regimens with platins and taxanes have been the mainstay of treatment.¹⁵ Sequential combination chemotherapy with paclitaxel/carboplatin/oral etoposide and gemcitabine/irinotecan has also been tried as an active treatment for patients with carcinoma of unknown primary.¹⁵

Targeted therapies offer promise for outcome improvement in patients with cancer of unknown primary, but this approach is hindered by lack of known molecular targets on which tumors are dependent for growth.¹⁷ Some studies have supported the clinical investigation of VEGF-targeted therapy for these types of cancers.^{17,18}

As with non-AIDS-defining cancers, the influence of T cell counts and HIV viral load remains uncertain. In fact, the literature presents contradictory information about the role of T cell count and HIV viral load for non-AIDS-defining cancers.^{24,25} Unfortunately there is no data available in relation to T cell counts, HIV viral loads, onset of HAART treatment, and outcomes in HIV-infected patients with cancer of unknown primary site.

Current studies suggest that patients with HIV-associated non-AIDS-defining cancers, particularly those with robust CD4 counts, should be treated with similar approaches to their HIV-negative counterparts.²⁴ The lack of strong data on treatment options and response to treatment for patients with cancer of unknown primary makes this proposition an attractive one, even though short and long term outcomes have not been studied.

In relation to HAART therapy, it appears that it is a protective factor against the appearance of certain non-AIDS-defining cancers.^{20,21,22,23} Based on these results, some authors have suggested that, in view of the fact that there are newer antiretroviral regimens with more favorable toxicity and resistance profiles compared to prior regimens, initiating therapy at higher CD4 cell counts may be a better option in HIV-infected patients with non-AIDS-defining cancers.^{24,25} Whether the same rule applies for cancer of unknown primaries is still uncertain.

The use of promising targeted therapies for non-HIV-infected populations affected with cancer of unknown primary is under investigation. Whether these new therapies will work with the same effectiveness in HIV-infected patients, and the short and long term outcome, is still unknown.

There are still many uncertainties surrounding the complex relationship between cancer of unknown primary and HIV infection. More studies are needed to clarify the prevalence, behavior, cancer biology and dynamics, diagnosis, and treatment of cancer of unknown primary site in HIV-infected populations.❖

REFERENCES

1. Bedimo R. Non-AIDS-defining malignancies among HIV-infected patients in the highly active antiretroviral therapy era. *Current HIV/AIDS reports*. 2008; 5(3):140-149.
2. Martinez LJ, Lynch GR, Grimes RM. Non-Kaposi's cancer in HIV infected patients at an urban teaching hospital. *International Conference on AIDS*. 1998. 12: 1104.
3. Hainworth JD, Greco FA. Treatment of patients with cancer of an unknown primary site. *New England Journal of Medicine*. 1993. Volume 329:257-263.
4. Pentheroudakis G, Briasoulis E, Pavlidis N. Cancer of unknown primary site: missing primary or missing biology? *The Oncologist*. 2007; 12: 418-425
5. Wouw AJ, Jansen RLH, Speel EJM, Hillen HFP. The unknown biology of the unknown primary tumor: a literature review. *Annals of Oncology*. 2003. 14; 191-196.

6. Seve P, Sawyer M, Hanson J, Broussolle C, Dumontet C, Mackey JR. The influence of comorbidities, age, and performance status on the prognosis and treatment of patients with metastatic carcinomas of unknown primary site. *Cancer*. 2006. Volume 106, No 9.
7. Kiertiburanakul S, Likhitpongwit S, Ratanasiri S, Sungkanuparph S. Malignancies in HIV-infected Thai patients. *HIV Medicine*. 2007; 8, 322-323.
8. Hillen HFP. Unknown primary tumors. *Postgraduate Medicine*. 2000; 76: 690-693.
9. Mintzer DM, Warhol M, Martin AM, Greene G. Cancer of Unknown Primary: Changing Approaches. A Multidisciplinary Case Presentation from the Joan Karnell Cancer Center of Pennsylvania Hospital. *The Oncologist* 2004, 9: 330-338.
10. Demir H, Berk F, Raderer M, Plowman PN, Lassen U, Daugaard G, Clausen M, Bohuslavizki KH, Peters M, Harmer C, Malamitsi J, Aktolun C. The role of nuclear medicine in the diagnosis of cancer of unknown origin. *The Quarterly Journal of Nuclear Medicine and Molecular Imaging*. 2004; 48: 164-173.
11. Rades D, Kuhnel G, Wildfang I, Borner AR, Schmoll HJ, Knapp W. Localised disease in cancer of unknown primary (CUP): The value of position emission tomography (PET) for individual therapeutic management. *Annals of Oncology*. 2001; 12:1605-1609.
12. Varadhachary GR, Talantov D, Raber MN, Meng C, Hess KR, Jatkoe T, Lenzi R, Spigel DR, Wang Y, Greco FA, Abbruzzese L, Hainsworth JD. Molecular profiling of carcinoma of unknown primary and correlation with clinical evaluation. *Journal of Clinical Oncology*. 2008. Volume 26, No 27.
13. Horlings HM, Van Laar RK, Kerst JM, Helgason HH, Wesseling J, Jacobus JM, Hoeven VD, Warmoes MC, Floore A, Witteveen A, Lahti-Domenici J, Glas AM, Veer JV, De Jong D. Gene expression profiling to identify the histogenetic origin of metastatic adenocarcinoma of unknown primary. *Journal of Cancer Oncology*. 2008. Volume 26 No 27.
14. Pentheroudakis G, Golfopoulos V, Pavlidis N. Switching benchmarks in cancer of unknown primary: From autopsy to microarray. *European Journal of Cancer*. 2007; 43: 2026-2036
15. Greco FA, Rodriguez GI, Shaffer DW, Hermann R, Litchy S, Yardley DA, Burris HA, Morrissey LH, Erland JB, Hainsworth JD. Carcinoma of unknown primary site: sequential treatment with Paclitaxel/Carboplatin/Etoposide and Gemcitabine/Irinotecan: A Minnie Pearl Cancer Research Network Phase II Trial. *The Oncologist*. 2004; 9: 644-652.
16. Karavasilis V, Malamou-Mitsi V, Briasoulis E, Tsanou E, Kitsou E, Kalofonos H, Fountzilas G, Fotsis T, Pavlidis N. Angiogenesis in cancer of unknown primary: clinicopathological study of CD34, VEGF and TSP-1. *BMC Cancer*. 2005; 5:25.
17. Pentheroudakis G, Pavlidis N. Perspectives for targeted therapies in cancer of unknown primary site. *Cancer Treatment Reviews*. 2006;32:637-644.
18. Massard C, Voigt JJ, Laplanche A, Culine S, Lortholary A, Bugat R, Theodore C, Priou F, Kaminsky MC, Lesimple T, Pivot X, Coudert B, Douillard JY, Merrouche Y, Fizazi K. Carcinoma of an unknown primary: are EGF receptor, Her-2/neu, and c-Kit tyrosine kinases potential targets for therapy? *British Journal of Cancer*. 2007; 97:857-861.
19. Oien KA, Evans TRJ. Raising the profile of cancer of unknown primary. *Journal of Clinical Oncology*. 2008. Volume 26, No 27.
20. Tomita M, Matsuzaki Y, Shimizu T, Hara M, Ayabe T, Enomoto Y, Onitsuka T. Squamous cell carcinoma of the hilar lymph node with unknown primary tumor: A case report. *Annals of Thoracic Cardiovascular Surgery*. 2008, Vol 14, No 4.
21. Jentasch-Ullrich K, Kalinski T, Roessner A, Franke A, Mohren M. Long-term remission in a patient with carcinoma of unknown primary site. *Chemotherapy*. 2006; 52:12-15.
22. Long JL, Engels EA, Moore RD, Gebo KA. Incidence and outcomes of malignancy in the HAART era in an urban cohort of HIV-infected individuals. *AIDS*. 2008; Feb 19:22(4):489-496.
23. Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, Grigg R, Hylton T, Pawlish KS, McNeel TS, Goedert JJ. Cancer risk in people infected with human immunodeficiency virus in the United States. *International Journal of Cancer*. 2008;123,187:187-194
24. Palella FJ, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, Holmberg SD. Mortality in the highly active antiretroviral therapy era. Changing causes of death and disease in the HIV outpatient study. *Journal of Acquired Immunodeficiency Syndrome*. 2006, Vol 43 No 1.
25. Cinti SK, Gandhi T, Riddell J. Non-AIDS-defining cancers: should antiretroviral therapy be initiated earlier? *The AIDS Reader*. 2008; 18.1 January.

Marco Ruiz is Assistant Professor, LSUHSC Section of Infectious Disease; Staff Physician, MCLNO HOP Clinic; and faculty Delta Region AETC.