JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of AIDS/HIV

Case Report

Anal Squamous Cell Cancer in a Patient with Human Immunodeficiency Virus Type 2 Infection: Report of a Case and Review of the Literature

Zola Nlandu[1#], Shayna Sarosiek[1], Qing Zhao[2], Gustavo Mercier[3], Angela Kuhnen[4], and Kevan L Hartshorn[1*]

[1]*Section of Hematology Oncology,*

[2]*Department of Pathology,*

[3]*Department of Radiology, and*

[4]*Department of Surgery, Boston University School of Medicine, Boston, MA, USA*

[#]*Current location Athens Regional Medical Center, Athens, GA, USA*

[*]*Corresponding author: Dr. Kevan L. Hartshorn, MD, Boston University School of Medicine EBRC 414 650 Albany Street Boston, MA 02118, Tel: 617-638-5638; Email: khartsho@bu.edu*

Received: 05-11-2016

Accepted: 06-24-2016

Published: 07-11-2016

Abstract

Infection with human immunodeficiency virus type 2 (HIV-2) is predominantly seen in West Africa, but has increasing incidence in the United States and Europe. Differentiating an HIV-2 infection from the more well-known human immunodeficiency virus type 1 (HIV-1) infection may be challenging, but is an important distinction due to differences in the natural history and treatment of the two viral infections. Anal squamous cell carcinoma (ASCC) is known to be a Human Papilloma Virus (HPV) driven malignancy, but is not classified as an AIDS defining illness, despite an increased incidence of ASCC in HIV-seropositive individuals. The utilization of chemoradiotherapy and the appropriate anti-retroviral therapy (ART) is the recommended treatment for squamous cell anal carcinoma in HIV-seropositive individuals. We present a case of a 76-year-old female emigrant from Cape Verde, who presented with a history of anal pain and rectal bleeding. She was initially considered to be HIV-1 positive, but was then lost to follow up and seven years later she presented with stage IIIB ASCC. Interestingly, on her second presentation to medical care she was found to be HIV-2 positive and HIV-1 negative during screening labs conducted prior to commencing chemoradiotherapy. Here we discuss the challenges in treatment of ASCC in this patient and in diagnosis and treatment of HIV-2.

Keywords: Human Papilloma Virus; Anal Cancer; West Africa; HIV-1; HIV-2; ART

Introduction

Anal squamous cell carcinoma (ASCC) is a relatively uncommon malignancy of the gastrointestinal tract [1]. Though not classified as an AIDS defining illness, it is more prevalent in individuals infected with HIV-1 [2-5]. ASCC incidence remains high in HIV positive subjects in the era of highly active ART [4]. In fact, there remains concern of under treatment of cancers in HIV positive subjects [2]. To our knowledge cases of ASCC occurring in HIV-2 infected patients have not been reported. The relationship of cervical cancer or high grade squamous intra-epithelial lesions to both HIV-1 and HIV-2 has been described and these are like ASCC in being strongly linked to high risk human papilloma virus (HPV) [6, 7]. HIV-2 infection is less likely to lead to profound immunodeficiency than HIV-1 infection; however, patients who are HIV-2-seropositive can go on to develop immunodeficiency and similar opportunistic infections and neoplasms as their HIV-1-seropositive counterparts [8, 9]. Of note, Europe and the United States have seen increasing number of cases of the HIV-2 though it is still predominantly seen in West Africa [9, 10]. Consequently, it is important to be aware of factors which should raise suspicion for HIV-2, diagnostic challenges in attaining a confirmatory diagnosis of HIV-2, and the fact that patients diagnosed with HIV-2 can develop maladies similar to those with HIV-1. We present a case of a woman with HIV-2 infection and ASCC that illustrates the difficulties in diagnosis and management of HIV-2 and treatment of cancer in this setting.

Case Report

A 76-year-old female patient, who emigrated from Cape Verde, initially presented to our hospital with complaints of anal pain, accentuated with defecation, and bleeding per rectum. At the time of presentation, she denied any constitutional symptoms or family history of colorectal cancer. She also reported having had an unremarkable colonoscopy 12 years prior in Cape Verde.

A digital rectal examination done at that time was significant for an ulcerated lesion located in the left lateral anal margin with no palpable lymphadenopathy. She underwent a colonoscopy and anoscopy with biopsy. The anal lesion revealed extensive high grade squamous dysplasia/carcinoma in situ, focally extending into the biopsy tissue edges, but with no definite invasive carcinoma seen (Figure 1A).

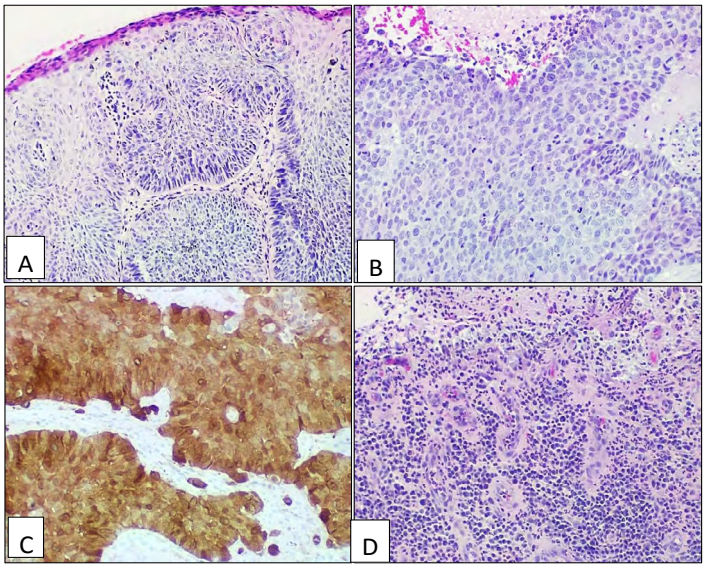

Figure 1. Hematoxylin and eosin (H&E) stain of initial anal biopsy in 2008 shows high grade squamous dysplasia/carcinoma in situ (A). H &E stains of the anal biopsy in 2015 shows invasive poorly differentiated squamous carcinoma with basaloid differentiation, tumor necrosis and increased mitotic figures (B)). P16 protein is strongly positive in the invasive carcinoma (C) by immunohistochemistry. H &E stain of the most recent anal biopsy in 2016 status post treatment revealed inflamed granulation tissue and stromal fibrosis, no residual carcinoma (D).

At that time she was also found to be HIV-1 positive on a preliminary enzyme linked immunoassay. This diagnosis was later confirmed via western blot which was strongly positive for HIV type 1 antibodies to gp160, p24, p31 and p40. Her CD4 count was 832/mm^3 and HIV viral load was < 75 copies/ml. She denied any history of intravenous drug use and had not been sexually active in over six years since her husband died. She noted that her husband had multiple sexual partners and did not use condoms with her. She returned to Cape Verde without initiating treatment with anti-retroviral therapy (ART) and was lost to follow-up.

The patient presented again to our institution seven years later. On this occasion, she gave a 6 month history of perianal pain, inability to sit comfortably, and fecal incontinence. On digital rectal examination, she was noted to have an ulcerated lesion in the left lateral anal margin and palpable bilateral inguinal lymphadenopathy. A repeat biopsy showed invasive and poorly differentiated squamous cell carcinoma with basaloid features (Figure 1B). Immunohistochemical stain for p16 protein was positive, indicative of association with high risk HPV (figure 1C). She had a PET-CT scan demonstrating a mass lesion in the anal canal and enlarged bilateral inguinal nodes (Figure 2A and B). The anal lesion and inguinal nodes were hypermetabolic as reflected in increased standardized uptake value (SUV) (see figure legend). The clinical staging based on the PET CT scan was stage IIIB (T3N3M0).

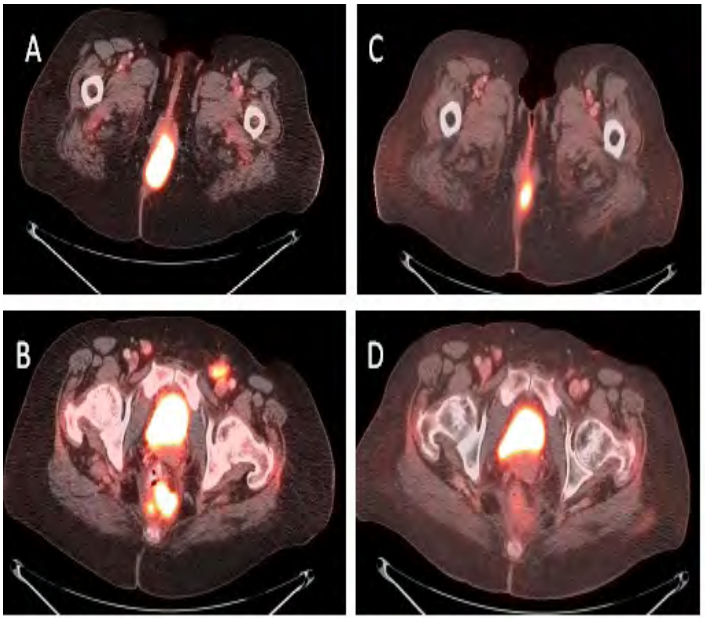

Figure 2. Axial images from 18-FDG PET/CT scans of the pelvis before (A) and after therapy (B) at the level of the rectum/anus. The anal tumor is hypermetabolic with pretherapy SUVmax of 20 and posttherapy SUVmax of 8.5. The cephalocaudal extent of the tumor was 13cm before therapy and it decreased to 7.7cm. Axial images from 18-FDG PET/CT scans of the pelvis before (C) and after therapy (D) at the level of inguinal lymph nodes. Hypermetabolic metastatic lymphadenopathy is seen on the left side with SUVmax of 6.3 in a lymph node with a short axis of 1.1cm. This resolved after therapy.

Contrary to her prior testing, screening laboratory tests prior to commencing chemotherapy and radiation confirmed that she was HIV-2 positive and HIV-1 negative. The initial HIV-1 antibody screen was twice positive and unable to be differentiated by combined assay. Additionally the HIV-1 viral load and RNA were undetectable. A CD4 count of 783/mm^3 was noted. A Multispot test was performed at a reference

laboratory and this was positive for HIV-2 antibody and negative for HIV-1 antibody. Testing for HIV-2 proviral DNA was negative and the HIV-2 RNA viral load was positive at 13 copies/ml. Anti-retroviral therapy (ART) was commenced prior to chemoradiotherapy using dolutegavir 50 mg daily and emtricitabine-tenofovir 200-300mg daily.

Given her incontinence and potential challenges of undergoing chemoradiation with such a large anal lesion, laparoscopic diverting colostomy was performed prior to commencing chemoradiation. Repeat CD4 count performed two months after starting ART and prior to radiation was 1180/mm^3. She received the first cycle of chemotherapy with mitomycin 10 mg/m^2 on day one and 5Fluorouracil 1000 mg/m^2 per day on days one through four of radiation. Unfortunately, on day 15 of radiation she developed bacteremia with *Escherichia coli* and *Streptococcus constellatus.* At this time she had a platelet count of 34,000/µl and absolute neutrophil count of 2,700/µl. Her implanted venous access device had to be removed due to the bacteremia. She completed her full course of radiation (5400 gray) on schedule despite the infection complications and local dermatologic toxicity. However, due to port removal, 5-FU was replaced with capecitabine during the second cycle and the dose of mitomycin-C was reduced to 5 mg/m^2 due to the degree of thrombocytopenia.

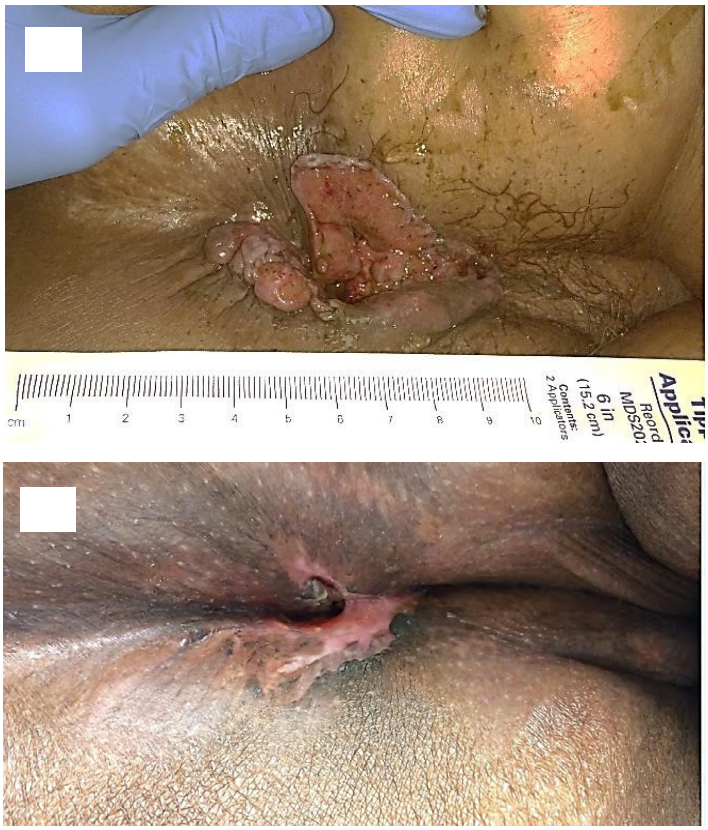

Figure 3. Photographs of the patients anal lesion prior to chemoradiation (A) and six months after treatment (panel B).

A repeat CD4 count, performed approximately 2 months after completion of chemoradiation, was 367/mm^3. Approximately 5 months after completing chemoradiation the CD4 count remained relatively stable at 333/mm^3. The patient reported compliance with ART, as well as marked improvement in pain and local anal symptoms. A PET-CT scan six weeks after completion of chemoradiotherapy, showed a partial response to therapy with residual tumor within the anus (Figure 2C and D). Repeat anoscopy 8 weeks after completion of treatment showed significant improvement, with a residual 4 by 4 cm ulceration in the anus. Anoscopy was again performed at approximately six months post completion of chemoradiation, and this showed further resolution of the ulceration. Biopsy performed at this time showed inflamed granulation tissue with lymphoplasmacytic inflammation with no residual tumor Figure 1D). Stromal fibrosis and ulceration are consistent with treatment effect. Figure 3 shows the appearance of the anal mass prior to chemoradiation and at six months after treatment (time of final biopsy specimen).

Discussion

ASCC is a relatively uncommon malignancy, accounting for 1.5% to 2.5% of cancers originating from the GI tract [3]. Mirroring cervical cancer, more than 90% of cases of anal cancer are the result of persistent infection with HPV [11]. Individuals infected with HIV-1 are at a higher risk of developing ASCC. The incidence of anal cancer is 40 to 80 times higher in the HIV-1 positive population [5]. This finding, has been attributed to similar routes of exposure to HIV and HPV and the persistence of HPV in HIV-1 positive patients, as opposed to their immunocompetent counterparts [5, 11].

Treatment of ASCC has been studied extensively in HIV-1 negative and positive subjects and the standard of care has been combined chemoradiation with mitomycin-C and 5-fluorouracil given in two cycles on days 1 and 28. There is some controversy as to whether mitomycin should be replaced with cisplatin in HIV1 positive patients, due to the increased myelosuppressive effects of mitomycin [12, 13]. However, a large trial comparing these two regimens in non-HIV infected patients found superior survival and reduced need for salvage surgery in the mitomycin containing treatment arm [14, 15]. In addition, recent studies show similar tolerance of the mitomycin based regimen in HIV positive and negative patients in the HAART era [16-19]. We reported on dose painted radiation in ASCC and this approach improves tolerance of chemoradiation [20].

Based on these findings we proceeded with the standard mitomycin-based regimen in our patient. She did have a greater degree of thrombocytopenia than is typically expected and developed bacteremia after cycle one of chemotherapy. The bacteremia, in particular the *Streptococcus constellatus* infection, may have resulted in part from the large, necrotic

tumor. Note that *Streptococcus constellatus* – like *Streptococcus bovis* and *clostridium septicum* - is associated with colorectal cancer [21, 22]. However, it is also likely that her infection was a reflection of immune compromise due to her HIV-2 infection. Recent phase II studies have observed replacement of infusional 5FU with capecitabine during radiation of anal squamous cell cancer [23-25]. These trials showed similarly high survival rates to historical controls in which 5FU was used. Based on these data we replaced 5FU with capecitabine for the second cycle of therapy.

HIV-2 has a higher prevalence in West Africa and that an increasing number of cases are being observed in Europe and the United States [9]. Cape Verde has close ties with Senegal where HIV 2 is prevalent and this may explain the prevalence of HIV 2 in Cape Verde [26]. Of interest HIV-2 infections in Cape Verde are predominantly subtype A and, in previously untreated patients, did not show resistance mutations in a recent survey [26]. In the New England states such as Massachusetts and Rhode Island, where over 200,000 individuals from Cape Verde reside, there have been some reported cases of HIV-2. According to the Center for Disease Control (CDC), during 1988 to June 2010, a total of 242 HIV-2 cases were reported from the various health departments throughout the United States [10]. One hundred and sixty six of the cases (66%) reported met the working definition of HIV-2 and were concentrated in the Northeast. The majority of these cases (81%) occurred in individuals born in West Africa. Consequently, testing for HIV-2 should be considered in patients from West Africa or Cape Verde who have symptoms or signs suggestive of HIV infection or known risk factors [7].

HIV-2 has lower infectivity than HIV-1, it is also less virulent than HIV-1, and associated with higher CD4 counts and consequently a longer asymptomatic phase and slower progression to AIDS [8]. However, if patients with HIV-2 infection are not correctly identified or do not receive adequate treatment and their CD4 cell count diminishes, they will develop illnesses similar to those seen in HIV-1 patients [9]. Our case illustrates a possible association between HIV-2 infection and ASCC.

Diagnostic challenges exist in the differentiation of HIV-1 and HIV-2 as illustrated in our case. Using current tests an initial immunoassay result which is positive for HIV antibodies but indeterminate as to subtype needs to be followed up with assays that can differentiate HIV-1 and HIV-2 [9]. Note that 60% of HIV-2-infected persons will repeatedly test reactive by HIV-1 whole virus lysate enzyme immunosorbent assay (EIA), as significant cross reactivity occurs between HIV-1 and HIV-2. Presently, Bio-Rad's Laboratories' Multispot test is the only FDA approved rapid test with the capability of differentiating HIV-1 and HIV-2 [9, 10]. This is in keeping with the 2014 CDC guidelines for HIV diagnostic testing (see CDC website). Even with a result deemed HIV-2 positive from this test, a supplemental confirmatory test is necessary to confirm a diagnosis of HIV-2. In our case additional confirmation was made using HIV-2 RNA testing.

These diagnostic challenges indeed have implications on the treatment of HIV positive individuals with ASCC. Distinguishing between HIV-2 and HIV-1 is important because their clinical management differs. No randomized clinical trial has assessed the efficacy of specific ART regimens in HIV-2 infected patients. However, HIV-2 is intrinsically resistant to some commonly used classes of antiretroviral medications [27], namely non-nucleoside reverse transcriptase inhibitors and enfurviritde. Currently, the 2013 treatment guidelines released by the World Health Organization (WHO) state that a triple nucleoside regimen or nuceloside reverse transcriptase inhibitors plus a protease inhibitor should be used in the initial management HIV-2 infected individuals [27]. As in the case of other HIV related malignancies it is felt to be important to begin anti-retroviral therapy prior to intensive chemotherapy treatment.

HIV-2 plasma RNA levels and CD4 cell counts, can be monitored just as is recommended for HIV-1. However, in the United States there are currently no commercially available or FDA approved assays for quantification of HIV-2 RNA. Such testing is needed to improve the care of HIV-2-infected individuals. Chemoradiation independently lowers CD4 counts complicating follow up in a case like ours. A recent study showed that the drop in CD4 count post chemoradiation for ASCC in HIV-1 subjects was sustained but was not associated with increased incidence of HIV-related morbidities [16].

Conclusion

To our knowledge this is the first reported case of ASCC in a patient with HIV-2 infection. The case illustrates the need for increased awareness of HIV-2 testing in patients from endemic areas, since the incidence is increasing in the United States and Europe. In addition the case suggests that screening for ASCC should be considered for patients with HIV-2, similar to recommendations for HIV-1. This recommendation would hold for patients with relatively preserved CD4 counts (as in our case). The case also highlights the challenges associated with accurate diagnosis of HIV-2 infections and illustrates the importance of having this diagnosis prior to treatment in order to institute appropriate anti-retroviral therapy as well as anticipate potential complications that can occur in these patients. The patient was successfully treated despite myelosuppression and serious infection during treatment.

References

1. Wilkes G, Hartshorn K. Clinical update: colon, rectal, and anal cancers. Semin Oncol Nurs. 2012. 28(4): e1-22.

2. Suneja G, Shiels MS, Angulo R, Copeland GE, Gonsalves L et al. Cancer treatment disparities in HIV-infected individuals in

the United States. J Clin Oncol. 2014. 32(22): 2344-2350.

3. Corti M, Villafañe MF, Marona E, Lewi D. Anal squamous carcinoma: a new AIDS-defining cancer? Case report and literature review. Rev Inst Med Trop Sao Paulo. 2012, 54(6): 345-348.

4. Piketty C, Selinger-Leneman H, Bouvier AM, Belot A, Mary-Krause M et al. Incidence of HIV-related anal cancer remains increased despite long-term combined antiretroviral treatment: results from the french hospital database on HIV. J Clin Oncol. 2012, 30(35): 4360-4366.

5. Dandapani SV, Eaton M, Thomas CR Jr, Pagnini PG. HIV-positive anal cancer: an update for the clinician. J Gastrointest Oncol. 2010, 1(1): 34-44.

6. Hanisch RA ,Sow PS, Toure M, Dem A, Dembele B et al . Influence of HIV-1 and/or HIV-2 infection and CD4 count on cervical HPV DNA detection in women from Senegal, West Africa. J Clin Virol. 2013, 58(4): 696-702.

7. Hawes SE, Critchlow CW, Sow PS, Toure P, N'Doye I et al. Incident high-grade squamous intraepithelial lesions in Senegalese women with and without human immunodeficiency virus type 1 (HIV-1) and HIV-2. J Natl Cancer Inst. 2006, 98(2): 100-109.

8. Azevedo-Pereira JM, Santos-Costa Q. HIV Interaction with Human Host: HIV-2 As a Model of a Less Virulent Infection. AIDS Rev. 2016, 18(1): 44-53.

9. Campbell-Yesufu OT, Gandhi RT. Update on human immunodeficiency virus (HIV)-2 infection. Clin Infect Dis 2011. 52: 780-787.

10. Centers for Disease Control and and Prevention. HIV-2 Infection Surveillance--United States, 1987-2009. MMWR Morb Mortal Wkly Rep. 2011. 60(29): 985-988.

11. Marin-Muller C, Li M, Chen C, Yao Q. Current understanding and potential immunotherapy for HIV-associated squamous cell carcinoma of the anus (SCCA). World J Surg. 2009, 33(4): 653-660.

12. Alfa-Wali M, Allen-Mersh T, Antoniou A, Tait D, Newsom-Davis T. Chemoradiotherapy for anal cancer in HIV patients causes prolonged CD4 cell count suppression. Ann Oncol. 2012, 23(1): 141-147.

13. Grew D, Bitterman D, Leichman CG, Leichman L, Sanfilippo N et al. HIV Infection Is Associated With Poor Outcomes for Patients With Anal Cancer in the Highly Active Antiretroviral Therapy Era. Diseases of the colon and rectum. 2015, 58(12): 1130-1136.

14. Gunderson LL, Winter KA, Ajani JA, Pedersen JE, Moughan J et al. Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol. 2012. 30(35): 4344-4351.

15. Chin JY, Hong TS, Ryan DP. Mitomycin in anal cancer: still the standard of care. J Clin Oncol. 2012, 30(35): 4297-301.

16. Fraunholz IB, Haberl A, Klauke S, Gute P, Rödel CM. Long-term effects of chemoradiotherapy for anal cancer in patients with HIV infection: oncological outcomes, immunological status, and the clinical course of the HIV disease. Dis Colon Rectum. 2014. 57(4): 423-431.

17. White EC, Khodayari B, Erickson KT, Lien WW, Hwang-Graziano J et al. Comparison of Toxicity and Treatment Outcomes in HIV-positive Versus HIV-negative Patients with Squamous Cell Carcinoma of the Anal Canal. Am J Clin Oncol. 2014, epub.

18. Hauerstock D, Ennis RD, Grossbard M, Evans A. Efficacy and toxicity of chemoradiation in the treatment of HIV-associated anal cancer. Clin Colorectal Cancer. 2010, 9(4): 238-242.

19. Seo Y, Kinsella MT, Reynolds HL, Chipman G, Remick SC, Kinsella TJ. Outcomes of chemoradiotherapy with 5-Fluorouracil and mitomycin C for anal cancer in immunocompetent versus immunodeficient patients. Int J Radiat Oncol Biol Phys. 2009. 75(1): 143-149.

20. Kachnic LA, Tsai HK, Coen JJ, Blaszkowsky LS, Hartshorn K et al. Dose-painted Intensity-modulated Radiation Therapy for Anal Cancer: A Multi-institutional Report of Acute Toxicity and Response to Therapy. Int J Radiat Oncol Biol Phys. 2012. 82(1):153-158.

21. Harnik IG. Pyogenic liver abscess presenting after malignant polypectomy. Dig Dis Sci. 2007, 52(12): 3524-3525.

22. Gjeorgjievski M, Alhalabi O, Kazanji N, Desai T. Clostridium septicum arthritis and aortitis in a patient with underlying colon cancer. QJM 2016, [Epub ahead of print].

23. Oliveira SC, Moniz CM, Riechelmann R, Alex AK, Braghirolli MI et al. Phase II Study of Capecitabine in Substitution of 5-FU in the Chemoradiotherapy Regimen for Patients with Localized Squamous Cell Carcinoma of the Anal Canal. Journal of gastrointestinal cancer. 2016, 47(1): 75-81.

24. Meulendijks D, Dewit L, Tomasoa NB, van Tinteren H, Beijnen, JH et al. Chemoradiotherapy with capecitabine for locally advanced anal carcinoma: an alternative treatment option. Br J Cancer. 2014. 111(9): 1726-1733.

25. Thind G, Johal B, Follwell M, Kennecke HF. Chemoradiation with capecitabine and mitomycin-C for stage I-III anal squamous cell carcinoma. Radiat Oncol. 2014, 9: 124.

26. de Pina-Araujo II, Guimarães ML, Bello G, Vicente AC, Morgado MG. Profile of the HIV epidemic in Cape Verde: molecular epidemiology and drug resistance mutations among HIV-1 and HIV-2 infected patients from distinct islands of the archipelago. 2014. PLoS One. 2014, 9(4): e96201.

27. Ekouevi DK, Tchounga BK, Coffie PA, Tegbe J, Anderson AM et al. Antiretroviral therapy response among HIV-2 infected patients: a systematic review. BMC Infect Dis. 2014, 14: 461.