Le Infezioni in Medicina, n. 2, 187-191, 2015

Spinal lesions by infectious spondylodiscitis and hepatocellular carcinoma presenting as spinal metastasis in an HIV-HCV co-infected patient

Lesioni vertebrali da spondilodiscite e metastasi di epatocarcinoma in un paziente con confezione da HIV-HCV

Gilda Tonziello[1], Romina Valentinotti[1], Fulvio Stacul[2], Donatella Giacomazzi[1], Roberto Luzzati[1]

[1]Infectious Disease Unit;
[2]Unit of Radiology,
University Hospital of Trieste, Trieste, Italy

INTRODUCTION

Intravenous drug use is a well-recognized risk factor for infectious spondylodiscitis, especially in HIV-infected patients [1, 2]. Back pain is the most common initial symptom, and fever is not invariably present. The differential diagnosis includes disc herniation, vertebral compression fracture, inflammatory spondyloarthropathies, degenerative or metastatic spinal diseases [3]. The latter can be associated with various cancers including hepatocellular carcinoma (HCC), a complication of hepatitis C virus (HCV)/HIV coinfection [6]. Moreover the introduction of highly active antiretroviral therapy (ART) has led to a decrease in AIDS related mortality and AIDS defining cancers including Kaposi's sarcoma, non-Hodgkin lymphoma and invasive cervical cancer. In contrast, the rates of various cancers including HCC have failed to decrease with ART, and to date represents the majority of cancers in HIV patient population [4, 5].

Corresponding author
Gilda Tonziello
E-mail: gildaton@hotmail.it

CASE REPORT

Here, we describe the case of a caucasian 51-year-old male with a history of intravenous drug use who was admitted to our hospital in July 2012 for back pain at the dorsal spine segment. His past medical history revealed seroconversion to HIV-1 in 1994, and to HCV in 1999. The patient enjoyed relatively good health although he continued to use intravenous illicit drugs even on replacement therapy with methadone. In 2007, laboratory data were the followings (Table 1): $CD4^+$ 960 cells/µl, $CD4^+$ cell percentage 33%, HIV RNA 17 000 copies/ml, HCV RNA 1.46 x 10^4 UI/ml. At that time, he had started the antiretroviral therapy (ART) regimen including tenofovir, lamivudine and unboosted fosamprenavir. Since the patient was diagnosed a severe anxious depressive syndrome, treatment of chronic hepatitis C had been excluded. In 2009, he underwent splenectomy for an abdominal trauma.

At hospital admission, in July 2012, the body temperature was 37°C and physical examination was unremarkable, except for hepatomegaly. No neurological deficit was found. The blood examinations showed the following abnormalities: serum C-reactive protein 61 mg/L (normal value <5

mg/L), white blood cells 25.2 x 10^3/µL, neutrophils 17.2x10^3/µL. In addition, $CD4^+$ cell count was 1866/µL, $CD4^+$ cell percentage 36%, HIV RNA undetectable (<50 copies/mL), and HCV RNA 1.28x10^5 UI/mL (Table 1). MRI of the spine showed gadolinium enhancement of T8-T9 vertebrae, discs and surrounding paravertebral soft tissues (Figure 1). An open biopsy of the spinal lesion was performed and the histological examination showed osteonecrosis with neutrophil and eosinophil infiltrate; the culture of biopsy sample turned out to be positive for *Pseudomonas aeruginosa,* sensitive to all anti-pseudomonas antibiotics. These results were consistent with the diagnosis of infectious spondylodiscitis. The patient was treated with targeted intravenous therapy initially with ceftazidime and ciprofloxacin for 3 weeks, then for the following 3 weeks ceftazidime was changed with amikacin once a day to continue the treatment as an outpatient, while oral ciprofloxacin was continued for a total of 5 months, with improvement of spinal symptoms and imaging abnormalities and normalization of C reactive protein. In March 2013, the patient referred worsening of the dorsal pain and right costal pain, then he performed a FDG-PET scan which showed an abnormal radionuclide concentration in T8-T9 facet joints, but no involvement of the disc and paravertebral soft tissues. This was consistent with the healing of spondylodis-

Table 1 - Biochemical and virological data of the patient.

	2007 *HAART start*	*July 2012* *Diagnosis of spondylodiscitis*	*March 2013* *End of antibiotic therapy*	*July 2013* *Diagnosis of HCC*
CD4 (cells/µL)	960	1866	2100	2560
CD4 (%)	33	36	35	35
HIV-RNA (copies/mL)	17000	Undetectable	Undetectable	
HCV-RNA (UI/mL)	$1{,}46x10^4$	$1{,}28x10^5$		
PCR (mg/mL)		61	<5	<5
WBC (cells/µL)		25000	11000	13070

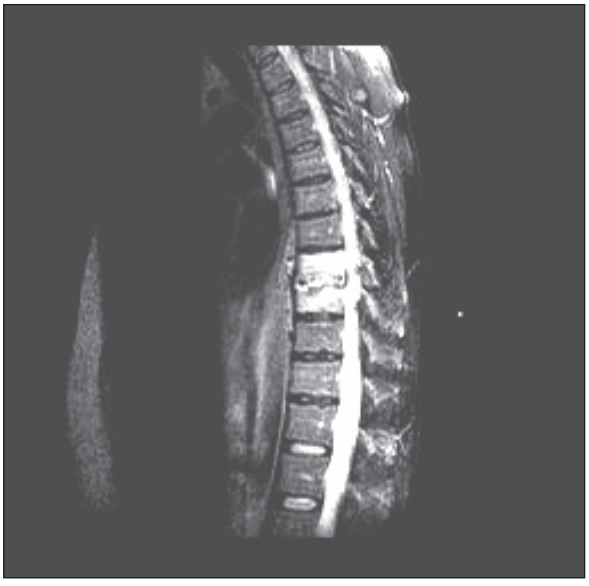

Figure 1 - MRI of the thoracic spine (fat sat T2 weighted image) in July 2012: changes consistent with spondylodiscitis at T8-T9 level. No other significant findings.

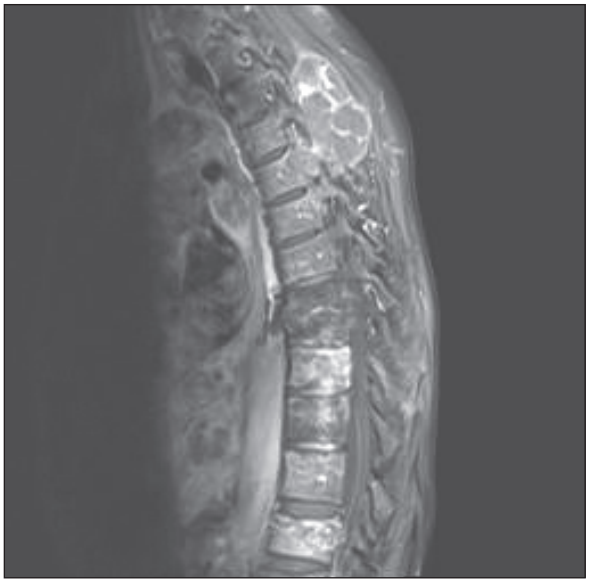

Figure 2 - MRI of the thoracic spine (contrasted fat sat T1 weighted images) in July 2013. Secondary deposits involving the vertebral body of T3-T6, T10-T12 and L1. The T3-T6 lesions largely involve adjacent soft tissues, as well. The fusion of T8-T9 is due to the previous spondylodiscitis.

citis. No abnormal radionuclide concentration was found in other anatomic sites. In May 2013, the patient was receiving his ART regimen and methadone. Laboratory data showed $CD4^+$ cell count 2587/μL, $CD4^+$ cell percentage 35%, HIV RNA undetectable, and serum alpha fetoprotein within the normal range, as well. The liver ultrasound didn't show focal lesions. Then the patient continued to complain of worsening back pain. In July 2013, the MRI of the spine revealed several gadolinium-enhancing vertebral lesions in the T3-T6, T10-T12, and L1 segments (Figure 2). In addition, the chest CT scan showed multiple contrast-enhanced costal arch lesions near the vertebral alterations described above. One of such lesions was targeted for a percutaneous TC-guided biopsy whose histology revealed poorly differentiated cancer cells. The immunohistochemical reaction for cytoplasmic TTF-1 was diffusely positive, an immunophenotypic profile typical of HCC. In fact, the TC scan of the abdomen showed a contrast-enhanced lesion (8 cm in diameter) at the VIII segment of liver, with surrounding multiple smaller satellite nodular lesions. Even though treated with sorafenib, the patient died after 8 months from the HCC diagnosis.

DISCUSSION

The introduction of HAART has led to a decrease in the incidence of AIDS-defining cancers (Kaposi's Sarcoma, Non-Hodgkin's lymphoma and invasive cervical cancer). On the other hand, an increase in the incidence of non AIDS-defining cancers, including carcinoma of the anus, testis, lung, colon, Hodgkin disease and hepatocellular carcinoma (HCC) has been reported [4, 5].

Focusing on HCC, a prospective study performed by the French Mortavic group on a cohort of 25178 HIV positive patients revealed that deaths due to HCC rose 5-fold (4,7% to 25%) from 1995 to 2001 and that nearly all patients who died from HCC had an HCV co-infection [7].

These data have been confirmed by Giordano et al. who conducted a retrospective cohort study on 11678 HIV-only and 4761 HCV-HIV coinfected patients reporting that coinfected patients had an hazard ratio for cirrhosis of 9.24 compared with HIV-only, and an hazard ratio for HCC of 5.35 compared with HIV-only patients [8].

On the other hand, Di Benedetto et al. reported that in the HAART era HIV co-infection is not associated with a higher incidence of HCC in hepatitis C cirrhotic patients. In fact in their prospective cohort study conducted in hepatitis C cirrhotic patients with and without HIV co-infection between 1999 and 2010 they revealed that the incidence of HCC in HIV-HCV co-infected patients and HCV mono-infected patients was 1.54 (95% confidence interval = 0.5 to 3.6) and 3.03 (95% confidence interval = 1.22 to 6.23) cases per 100 person-year respectively [9].

These results have not been confirmed by Kramer et al. who recently published a restrospective cohort study on U.S. veterans where the risk of HCC in HCV- and HIV-coinfection was higher than HCV monoinfection; in fact in this study the overall age-adjusted incidence rate of HCC in monoinfected patients was 2.99/1000 person-years vs. 4.44/1000 person-years in coinfected patients. In the latter ones, presence of cirrhosis and a recent low CD4 cell count <200 were associated with an increased risk for HCC [10] .

Moreover HCC seems to have a more rapid evolution in HIV-HCV coinfected patients than in HCV monoinfection. In fact in a multivariate analysis performed in 2004 by the Italian cooperative group on AIDS and Tumours (GICAT) in 41 cases of HCC in HIV positive individuals (from a joint Italian and Spanish database) compared with 384 HIV-negative controls, the HIV patients with HCC were much younger at presentation (age 40-46 vs 60-70) and had more advanced infiltrating disease; in this study they observed also a trend to more advanced cirrhosis at presentation in the HIV positive population [11].

Also in our patient the HCV-associated HCC resulted to be very rapidly evolving despite effective ART regimen; in fact in the present case the neoplastic lesions were identified by neither the FDG-PET scan nor the liver ultrasound performed almost 4 and 2 months before the diagnosis of the metastatic lesions, respectively. In our opinion there is no link between the previous spondylodiscitis and the development of HCC metastasis, as different vertebral sites were involved.

Treatment of chronic hepatitis C for patients with HIV infection is essential to prevent the transition to liver cirrhosis, the development of HCC and liver failure. Interferon plus ribavirine therapy reduces liver related complications and mortality in

patients with sustained virological response [12]. Anyway the poor tolerability of Peg-IFN + RBV double therapy and of triple therapy with Peg-IFN + RBV + boceprevir or telaprevir has been a serious obstacle to treating chronic hepatitis patients with HIV/HCV coinfection. New interferon-free antiviral therapies for chronic hepatitis C in HIV infected patients are under investigation. Sulkowski et al. found rates of sustained virological response of 76% in patients with HCV-genotype 1, 88% in those with genotype 2 and 67% in those with genotype 3 coinfected with HIV who received the oral, interferon-free combination of sofosbuvir and ribavirin [13]. In the phase II COSMOS trial, where patients were treated with SMV + SOF with or without RBV, SVR was achieved in 92% previous non-responders with METAVIR scores F0-F2 and 94% previous non-responders and treatment-naive patients with METAVIR scores F3-F4 [14]. Among interferon-free therapeutic regimens for treatment of genotype 1 chronic hepatitis C in HIV coinfection under investigations are also the combination daclatasvir + simeprevir +/- ribavirin in the LEAGUE-1 trial and paritaprevir/r, ombitasvir, dasabuvir and RBV in the Turquoise-I trial. Preliminary data of both trials have shown good rates of sustained virological response [15, 16].

In conclusion this clinical case report shows how hepatocarcinoma might have a fast progression to a metastatic disease in a patient with chronic hepatitis C and HIV infection. The hope is that in the next future all these new interferon free regimens will change the clinical outcome of chronic hepatitis C-HIV coinfected patients, thanks to their high rates of sustained virological response in patients with cirrhosis, as well.

Conflicts of interest and source of funding

No conflict of interest and source of funding were declared from all authors.

Keywords: HIV-HCV coinfection, hepatocellular carcinoma, spondylodiscitis.

SUMMARY

Back pain and spine tenderness over the involved spine segment are common clinical findings of a number of relative benign conditions. However, back pain may be the presenting symptom of vertebral metastases in patients with systemic cancer, including hepatocellular carcinoma, a not uncommon complication in HCV-HIV infected patients. We describe a case of a 51-year-old intravenous drug user with HIV and HCV co-infection who developed dorsal spondylodiscitis due to *Pseudomonas aeruginosa*, which improved following antibiotic therapy. Three months after the end of therapy, the patient referred recurrence of back pain. The MRI showed different vertebral lesions of the dorsal spine and costal arch which turned out to be hepatocellular carcinoma metastasis at the histological examination. The patient had never been treated with the interferon-ribavirine combination therapy because of a major depressive syndrome. Interferon-free regimens are urgently required for HIV-HCV coinfected patients, especially when interferon-based regimens are contraindicated.

RIASSUNTO

La rachialgia può essere il sintomo di varie patologie relativamente benigne, ma si può presentare anche come sintomo d'esordio di metastasi vertebrali da varie neoplasie primitive, incluso l'epatocarcinoma, una complicanza non infrequente nei pazienti con confezione HIV-HCV.

Di seguito riportiamo il caso clinico di un paziente di 51 anni, tossicodipendente, con coinfezione da HIV e HCV che ha sviluppato una spondilodiscite da Pseudomonas aeruginosa, *trattata con successo con terapia antibiotica mirata. Dopo tre mesi dal termine della terapia antibiotica il paziente aveva presentato una recrudescenza della rachialgia. La RMN eseguita in tale occasione rivelava numerose lesioni vertebrali e costali, che all'esame istologico risultavano metastasi di epatocarcinoma. Il paziente non era mai stato trattato in precedenza per epatite cronica da HCV, in quanto affetto da depressione maggiore, che controindicava il trattamento con PEG-IFN. Questo caso suggerisce quanto sia importante l'introduzione di regimi antivirali per l'epatite cronica da HCV senza interferone, in particolar modo per quei pazienti in cui quest'ultimo farmaco sia controindicato per la presenza di comorbidità. Inoltre, questo caso sottolinea l'importanza della biopsia e dell'esame istologico nella diagnosi differenziale delle lesioni vertebrali, in particolar modo nei pazienti con infezione da HIV.*

REFERENCES

[1] Sobottke R., Zarghooni K., Krengel M., et al. Treatment of spondylodiscitis in human immunodeficiency virus-infected patients: a comparison of conservative and operative therapy. *Spine* 34, E452-E458, 2009.
[2] Siewe J., Oppermann J., Eysel P., Zarghooni K., Sobottke R. Diagnosis and treatment of spondylodiscitis in HIV-positive patients. *Acta Orthop. Belg*. 79, 475-482, 2013.
[3] Cottle L., Riordan T. Infectious spondylodiscitis. *J. Infect*. 56, 401-412, 2008.
[4] Lewden C., May T., Rosenthal E., et al. Changes in causes of death among adults infected by HIV between 2000 and 2005: the "Mortalité 2000 and 2005" surveys (ANRS EN19 and Mortavic). *J. Acquir. Immune Defic. Syndr*. 48, 590-598, 2008.
[5] Palella F.J. Jr, Baker R.K., Moorman A.C., et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J. Acquir. Immune Defic. Syndr*. 43, 27-34, 2006.
[6] MacDonald D.C., Nelson M., Bower M., Powles T. Hepatocellular carcinoma, human immunodeficiency virus and viral hepatitis in the HAART era. *World J. Gastroenterol.* 14,1657-1663, 2008.
[7] Rosenthal E., Poiree M., Pradier C., et al. Mortality due to hepatitis C-related liver disease in HIV infected patients in France (Mortavic 2001 study). *AIDS* 17, 1803-1809, 2003.
[8] Giordano T.P., Kramer J.R., Souchek J., Richardson P., El-Serag H.B. Cirrhosis and hepatocellular carcinoma in HIV-infected veterans with and without the hepatitis C virus: a cohort study, 1992-2001. *Arch. Intern. Med*. 164, 2349-2354, 2004.
[9] Di Benedetto N., Peralta M., Alvarez E., et al. Incidence of hepatocellular carcinoma in hepatitis C cirrhotic patients with and without HIV infection: a cohort study, 1999-2011. *Ann. Hepatol.* 13(1), 38-44, 2013.
[10] Kramer J.R., Kowalkowski M.A., Duan Z., Chiaio E.Y. The effect of HIV viral control on the incidence of hepatocellular carcinoma in veterans with hepatitis C and HIV coinfection. *J. Acquir. Immune Defic. Syndr*. 68(4), 456-462, 2015.
[11] Puoti M., Bruno R., Soriano V., et al. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. *AIDS* 18, 2285-2293, 2004.
[12] Berenguer J., Alvarez-Pellicer J., Martín P.M., et al. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. *Hepatology* 50, 407-413, 2009.
[13] Sulkowski M.S., Naggie S., Lalezari J., et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. *JAMA* 312(4), 353-361, 2014.
[14] Lawitz E., Sulkowski M.S., Ghalib R., et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. *Lancet* 384, 1756-1765, 2014.
[15] Zeuzem S., Hezode C., Bronowicki J.P.P., (LEAGUE-1 Study Team). Daclatasvir in combination with simeprevir ± ribavirin for hepatitis C virus genotype 1 infection. In Program and Abstracts of the 21st Conference on Retroviruses and Opportunistic Infections (CROI 2014), Boston, March 3-6, 2014, Abstract 28LB.
[16] Sulkowski M., Eron J., Wyles D. TURQUOISE-I: safety and efficacy of ABT-450/r/ombitasvir, dasabuvir, and ribavirin in patients co-infected with hepatitis C and HIV-1. In Program and Abstracts of the 20th International AIDS Conference. Melbourne, Australia, July 20-25, 2014, Abstract MOAB0104LB.