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CASE REPORT

HEPATIC AND SPLENIC TUBERCULOSIS IN A PATIENT WITH SEVERE IMMUNOSUPPRESSION AND NEUROLOGICAL COMPLICATIONS

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Summary

Introduction: Mycobacterium tuberculosis can be located in every organ of the human body developing specific tuberculosis histopathological aspects. Hepatic and splenic tuberculosis may be suspected in immunocompromised patients with hepatomegaly and splenomegaly, fever and elevated liver enzymes. Diagnosis is confirmed by culture of a pathological sample or by histological examination of a biopsy of the affected tissue or organ for M. tuberculosis.

Case report: 21 years old female known with HIV Infection Category C3 (CD4 -10 cells / mm3), treated with antiretroviral therapy (ART) since November 2014, diagnosed in January 2015 with Progressive Multifocal Leukoencephalopathy, tetra-ataxia, tetra paresis and secondary epilepsy with repeated admissions to an Infectious Department of our hospital for prolonged febrile syndrome, nausea and weight loss is thoroughly investigated for hepatosplenic abscesses identified by CT-scan. In May 2015 a liver biopsy performed in a Hospital in Bucharest and Real Time PCR identified M. tuberculosis 610,000 copies/ml and Rifampicin resistance gene present. Culture confirmed M. tuberculosis. Extended DST (after 60 days) revealed sensitivity just for Ethionamide - tuberculosis XDR (extensively resistant). Initial treatment with tuberculosis drugs according to regimen WHO category 1 was individualized for the identified resistances. ART was also modified because of resistance to Rifampicin. Her condition slowly improved with fever remission and improvement of biological inflammatory syndrome and neurological manifestations associating physical therapy and specialized treatment.

Conclusions: Extremely rare and very serious case of XDR TB with atypical localizations due to marked immunodeficiency. It represents a therapeutic challenge involving a multidisciplinary team and prolonged admissions in many specialized departments.

Résumé

Tuberculose hépato-splénique chez un patient présentant un déficit immunitaire sévère et des complications neurologiques

Introduction: Mycobacterium tuberculosis peut être localisée à tout organe, générateur de lésions tuberculeuses spécifiques. La tuberculose hépatique et splénique peuvent être suspectées chez les patients immunodéprimés ayant une hépatomégalie et une splénomégalie, fièvre et élévation des enzymes hépatiques. Le diagnostic de certitude est établi par des ponctions-bioptiques d'organes avec l'histopathologie et l'analyse microscopique et la culture spécifique à M. tuberculosis des fragments examinés.

Présentation de cas: Malade de 21 ans inclue à la catégorie de l'infection à VIH C3 (CD4 10 cellules/mm^3) traitée par la thérapie antirétrovirale (ARV) à partir de Novembre 2014, diagnostiquée en Janvier 2015 avec Leucoencéphalopathie Multifocale Progressive, Tétraparèse, Tetraataxie et épilepsie secondaire avec admissions répétées à notre hôpital à Craiova pour syndrome fébrile prolongé, nausées, perte de poids et investigations complexes pour les abcès hépatospléniques identifiés par imagerie. En mai 2015 la biopsie hépatique a été réalisée sous guidage imagistique à un hôpital à Bucarest, recherche menée afin d'identifier par PCR en temps réel du germe M. tuberculosis de 610.000 copies/ml et la présence du gène de résistance à la Rifampicine. La culture a confirmé la présence de M. tuberculosis. L'antibiogramme continué (après 60 jours) a révélé de la sensibilité seulement à l'Etionamide - Tuberculose XDR (ultrarésistante). Le traitement initial contre la tuberculose conformément au régime de la catégorie 1 de l'OMS été individualisé pour les résistances identifiées. La thérapie antirétrovirale a été modifiée en raison de la résistance à la rifampicine. L'evolution favorable a été lente avec la rémission de la fièvre et l'amélioration du syndrome inflammatoire biologique et de la manifestation neurologique par l'association de la thérapie

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physique et un traitement spécialisé.
Conclusions: C'est un cas de tuberculose XDR extrêmement rare et grave à localisation atypique qui se pose dans le contexte d'une immunodéficience marquée, ce qui représente un défi thérapeutique et implique la collaboration d'une équipe multidisciplinaire nécessitant une hospitalisation prolongée dans les services spécialisés.
Mots-clés: tuberculose hépatique, VIH, traitement de la tuberculose

BACKGROUND

Scale of the problem: millions affected and millions dead

In 1993, the World Health Organization (WHO) took an unprecedent step and declared tuberculosis a global emergency. Since then tuberculosis (TB) kills approximately 2 million people each year and the global epidemic is growing and becoming more dangerous. The breakdown in health services, the HIV/AIDS pandemic and the emergence of multidrug-resistant TB are contributing to the worsening impact of this disease. (1)

Tuberculosis (TB) is a top infectious disease killer worldwide and it is among the top 5 causes of death for women aged 15 to 44. In 2014 9.6 million people fell ill with TB and 1.5 million died from the disease (over 95% of TB deaths occured in low- and middle-income countries). An alarming rise was also seen in the number of MDR and XDR –TB. Globally in 2014 an estimated 480,000 people developed multidrug-resistant TB (MDR-TB). (2)

Human Immunodeficiency Virus type 1 (HIV) and Mycobacterium tuberculosis have become intertwined over the past few decades in a "syndemic" that exacerbates the morbidity and mortality associated with each pathogen alone. The emergence of human immunodeficiency virus type 1 (HIV) has exacerbated an already enormous number of cases of tuberculosis (TB) worldwide. TB affects HIV+ individuals throughout all phases of HIV infection and is the leading killer of HIV+ people: in 2015, 1 in 3 HIV deaths was due to TB. (2) (3)

The annual risk of active tuberculosis in patients with HIV-TB is 5-10% per year (compared to 5-10% for uninfected in a lifetime). This is why tuberculosis is the most common opportunistic infection and an important cause of death in HIV-infected patients, particularly in developing countries. (4) (5)

HIV/AIDS has also contributed to the relative rise in extra pulmonary TB (EPTB) rates, as the risk of extrapulmonary TB increases with decreasing CD4 counts. Over 50% of HIV /TB co-infected people present with extrapulmonary involvement including hepatic and splenic TB. (6)

According to the European Monitoring Report 2014 Tuberculosis, in 2012 in Romania were registered a total of 18,197 TB cases (85.2 per 100,000), of which 76.3% were new cases that have not received treatment before. About 232 cases (2.3%) co-infection HIV / TB and 530 cases of MDR-TB, of which 32 were XDR, were also reported in the same year. (7)

Clinical aspects of HIV/TB synergy

Starting with 1993, pulmonary TB was one of the definition criteria for the AIDS case in adults, while extra-pulmonary TB and disseminated atypical mycobacteriosis were considered definition criteria for the IV clinical stage of AIDS disease since 1987. (2) (3)

The TB clinical aspect for the HIV infected patients varies from the typical characteristics of the basic condition to those of the atypical disseminated illness. General symptoms are more prevalent (90% of patients have a significant deterioration of general condition, fever passes 39.0 C and is quasi-permanent in 85-95% of cases) associated with significant weight loss and important night sweats. Chronic cough, often productive is often associated with a form of extrapulmonary tuberculosis (in 40-80% of cases) and dyspnea is present in more than 50% of patients. Characteristics of TB and HIV/AIDS coexistence are: extrapulmonary TB, disseminated disease, rapid progression, lymphadenopathy, abscess formation, negative tuberculin skin test.

The epidemiological, clinical, immunological, and molecular biological studies done to date have revealed that HIV and TB synergize with one another at the population, individual, cellular, and molecular levels.

The nature, presentation and the clinical and radiological features of tuberculosis depend on the degree of immunosuppression. In those with relatively good immunity, good CD4+ cell counts and a low viral load, the manifestations and presenting symptoms of tuberculosis are essentially similar to those in HIV negative persons. As the immunocompetence decreases, there is an increasing incidence of atypical presentations of tuberculosis and diagnostic difficulties are posed by the rather non-specific presenting features which may be confused with those of other HIV related infections. These atypical forms of tuberculosis include rapid progression of clinical disease after infection and a high proportion of extrapulmonary, multisite and widely disseminated tuberculosis.(8)

Since the lung is one of the target organs for HIV, a

HIV-positive patient has 50-90% risk to make at least one pulmonary disease during the course of the disease. Because patients rarely have cavitary anatomic-radiologic lesions, the number of acid-fast bacilli in the sputum can be reduced and the efficiency of the smear-tests is low. Pulmonary TB in HIV positive patients can appear on X-ray film with focal infiltrates, diffuse infiltrates, cavities, pleural effusion, hilar or mediastinal adenopahties. There may be patients with normal chest X-ray, but with positive culture.

Most commonly, pulmonary tuberculosis is associated with a lymph node TB (30% of cases) and liver TB, but hepatomegaly, splenomegaly, skin lesions, ascites, meningeal syndrome can also be seen in patients with an advanced stage of HIV infection (CD4 $<200/mm^3$). (12) However, neurological, pleural, pericardial, abdominal involvement has been described and virtually every site in the body can be involved in HIV-positive patient. Definitive diagnosis of tuberculosis involves demonstration of M. tuberculosis by microbiological, cytopathological or histopathological methods. (13)

The evolution of tuberculosis for HIV patients, is generally favorable, but it varies, however, observing acute forms for those with severe immunosuppression or sub-acute and chronic forms which are characterized by the appearance at an early stage of HIV infection. (10)

CASE REPORT

We present the case of a 21 year old female known with HIV Infection Category C3 (CD4-10 cells/mm^3), treated with antiretroviral therapy (ART) since November 2014, diagnosed in January 2015 with Progressive Multifocal Leukoencephalopathy, Tetra-ataxia, Tetraparesis and Secondary Epilepsy considered to be due to HIV infection for which she received specific treatment. PML diagnosis was established after JC Virus was determined by PCR in cerebrospinal fluid.

Patient had repeated admissions in to Infectious Department of our hospital for prolonged febrile syndrome, nausea and weight loss (6 kg in 2 months) and also amenorrhea. Symptom onset apparently was associated with the onset of the neurological symptoms to which a non responsive to broad-spectrum antibiotic treatment prolonged febrile syndrome was added after 2 months.

Clinical exam showed a debilitated, underweight G = 40 kg (BMI = 14.70 kg / m^2) patient, feverish (Temperature = 39,8º C) with moderate dysarthria, mucosal and cutaneous pallor, multiple lymphadenopathies (axillaries, submandibular and laterocervical), decreased muscle strength, normal breath sounds but with the presence of some chest crackles, blood pressure = 110/70 mmHg, heart rate = 104/min, rhythmic heart sounds, palpable spleen and liver, normal diuresis, having difficulties holding her head up or walking without a support 2-3 steps, with moderate dysarthria, severe ataxia and visual deficits.

Imagistic exams performed in January 2015 had identified:

- *bulbo-pontine acute encephalitis area and a similar right cerebellar hemisphere lesion;*
- *encephalitis area in left cerebellar hemisphere with chronical aspect;*
- *aspects of ethmoid, sphenoid and maxillary chronical sinusitis.*

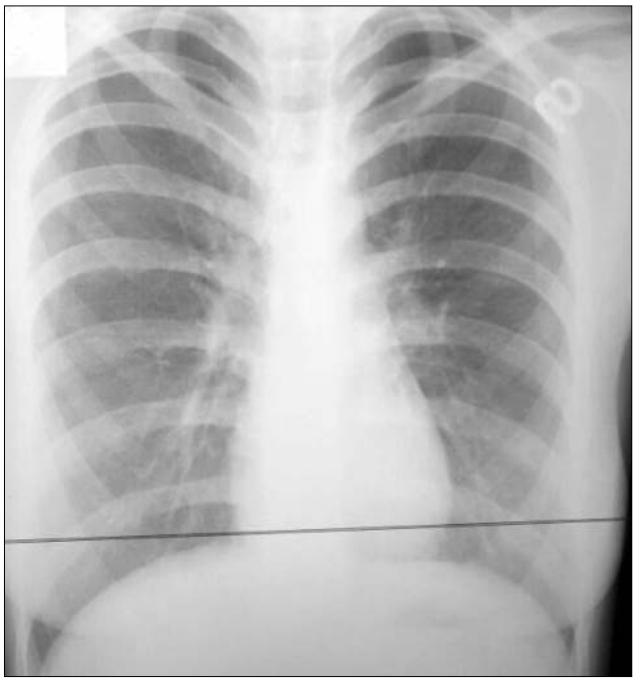

Figure 1 - Normal Chest X-ray (may 2015)

Blood tests in May 2015 showed a hemoglobin = 11.8 g/dl, H = 35.2%, WBC = 9000 / mm^3 (white blood cell), ESR = 86mm -1h, PLT = 441,000/mm^3 (platelet), CRP = 10.2 mg/dl (C reactive protein), Th lymphocytes (CD3 + CD4 +) = 184 cells/ml, ALT = 30U/L, creatinine = 0.6mg/dl

Chest X-ray in May 2015 was normal (Fig. 1).

Abdominal ultrasound exam described hepatomegaly and next to the gallbladder a well defined nodule of 50/30mm, slightly more hypoechoic than liver. The spleen was 12.2 cm/6.2 cm with the presence of one hypo echoic nodule in 1/3 medium part of the spleen of 18 mm diameter, with inhomogeneous structure, vaguely delineated. Pancreas and kidneys aspect was normal.

The patient was further investigated in Infectious Departments of 2 Hospitals in Bucharest where CT scan was repeated:

- *Chest: small pulmonary nodules in the right lung area;*
- *Abdomen: multiple nodular hepatic lesions suggestive of liver abscesses, 2 nodular spleen lesions of possible infectious etiology; important hepatic hilar lymphadenopathy (of 40/25mm) and hilar spleen lymphadenopathy (about 22 / 19mm);*
- *Pelvis: inhomogeneous aspect of the cervix and uterus that requires further investigation*
- *Skull: hyper dense lesion (Fig. 2) located in the right hemisphere of the cerebellum.*

Gynecological exam carried out later with Pap cytology exam has identified high-grade squamous intraepithelial lesions (HSIL). Bacteriological and mycological exams were negative.

Lymph node biopsies were performed (laterocervical and

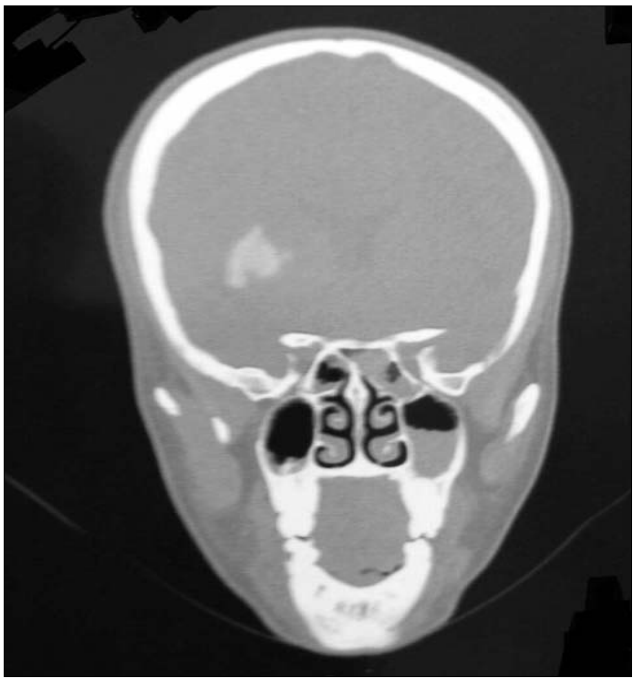

Figure 2- Skull MRI (May 2015)

axillary) and histopathology revealed hemorrhagic necrosis.

To establish the etiology of liver abscess a imaging-guided liver biopsy was performed in a Hospital in Bucharest. Gram smear described frequent polymorphonuclear cells, and the absence of gram-positive cocci, of gram negative bacilli or coccobacilli and subsequently negative cultures. Examination of biopsy piece using Real Time PCR identified M. Tuberculosis 610,000 copies/ml and Rifampicin resistance gene present. Culture revealed the presence of M. tuberculosis and extended DST revealed sensitivity after 60 days only for Ethionamide (resistance to isoniazid, rifampin, ethambutol, streptomycin, kanamycin, amikacin, ciprofloxacin) - diagnosis of XDR TB (extensively resistant).

Final diagnoses were:

1. *Disseminated XDR TB with multiple hepatic and splenic abscesses;*
2. *HIV Infection category C3;*
3. *Progressive Multifocal Leukoencephalopathy with tetraparesis and tetra-ataxia;*
4. *Secondary epilepsy;*
5. *High-grade squamous intraepithelial cervical lesion.*

Initial treatment with TB regimen WHO category 1 was individualized for the identified resistances as recommended by national guides of treatment for MDR-TB with Hydrazide, Pyrazinamide, Ethambutol, Cycloserine, Protionamida, Amikacin (doses calculated for patients' weight). Treatment was administered daily with good tolerability and fever remission and improvement of biological inflammatory syndrome. ART was also modified because of resistance to Rifampicin. Patient received Raltegravir, Kivexa, T20, Zidovudine (AZT), TDF (Tenofovir Disoproxil Fumarate) as recommended by the guides associated with Biseptol 1 tb/day for prophylaxis of Pneumocystis Carinii infection.

After receiving the result of extensive sensitivity testing she was transferred to Pneumology Institute from Bucharest to establish appropriate antituberculosis treatment regimen (medication category 5).

Her neurological condition had slowly improved at first with physical therapy sessions and specialized treatment with Depakine Chrono and Rivotril. She has't experienced any convulsive seizures in the last 7 months, but she is still suffering from moderate dysarthria and ataxia.

Current treatment is supervised by a multidisciplinary team and the evolution continues to be slowly favorable. Patient has gained weight (5 kg in last four months) and there has also been noticed a slight increase in the number of Th lymphocytes (CD3 + CD4 +).

Prognosis remains reserved.

Discussions

HIV is a driver for TB epidemics by increasing the incidence of TB and TB-related deaths in a population of immunodeficient individuals susceptible to both primary and reactivation TB. (18) Detection and treatment of HIV- TB infected patients is a priority of World Health Organization and a priority for TB control programs. International organizations are actively involved in the treatment and prevention of 2 diseases.

Preliminary data from observational and retrospective studies have suggested that TB accelerates the progression of disease in HIV and accelerates the virologic course of HIV. (19)

The relative risk of TB doubles in the first year after HIV infection, when CD4 counts are still preserved, and continues to increase during the years after seroconversion as CD4 counts decrease (20) HIV increases the risk of progression to active TB in both primary TB infection and the reactivation of latent TB. In populations of immunocompetent people, 3 to 5% will develop active TB in the first 2 years after TB infection HIV coinfection impairs the ability of the immune response to contain TB (discussed further below) and increases the likelihood of developing active TB during the initial period of TB infection. (21)

HIV alters the pathophysiology of hepatic TB. Hepatic TB in HIV infected and uninfected patients differs both clinically and pathologically. Immunocompromised HIV-infected patients not only have increased susceptibility to TB reactivation and dissemination but their manifestation tends to be more severe.

Hepatic tuberculosis – data to be considered

Tuberculous bacilli can reach the liver via hematogenous dissemination, generally from the lungs, or by local spread from the gastrointestinal tract. Among reported hepatic TB cases, miliary form accounted for 79% of the cases, while local hepatic TB accounted for 21% of cases. The source of miliary dissemination is from a pulmonary focus or from an extrapulmonary site such as an abdominal lymph node – bacilli reach the liver via the hepatic artery. Miliary TB is characterized by diffuse seeding of the liver with tubercles ranging from 0.6 to 2 mm in diameter situated in the

lobules of the liver. In local hepatic TB, also called tuberculoma, tubercles are greater than 2 mm in diameter and are usually situated near the portal triad region. A TB liver abscess commonly arises from local hepatic TB but may also occur following miliary hepatic TB. (6) The characteristic histological feature of both miliary and local forms of hepatic TB is the granuloma. Multiple granulomas may coalescence to form a large tuberculoma and caseation and liquefaction necrosis of a tuberculoma may lead to a tubercular abscess.

Clinical features of hepatic TB are nonspecific, which often leads to a diagnostic delay. Analysis of eleven hepatic TB case series revealed the most common presenting signs/symptoms here hepatomegaly (80%), fever (67%), respiratory symptoms (66%), abdominal pain (59,5%) and weight loss (57,5%). Other symptoms included spenomegaly (30%), ascites (23%) and jaundice (20%). Occasional increases in liver transaminases, alkaline phosphatase and gamma glutamyl transferase were also noticed. However, HIV-infected patients are more likely to have a concomitant pulmonary TB infection. (6) (22), (23)

Liver biopsy with mycobacterial culture is considered the most specific diagnostic test for hepatic TB. (14) Liver biopsies should be sent for both microbiological and histological evaluation. Microbiological methods include smear microscopy for acid – fast bacilli (AFB) and mycobacterial culture.

Because AFB smears and cultures have low sensitivity and granulomas are not specific polymerase chain reaction (PCR) has been recommended for diagnosing hepatic TB. PCR had a median sensitivity of 86% (range 30-100%) among hepatic TB case series. In addition PCR results can often be obtained earlier than mycobacterial culture results. (6) (15) (16)

Another potential diagnostic tool is the Xpert MTB/RIF assay, a rapid nucleic amplification assay which has been approved for diagnosing pulmonary TB from sputum sample and is also being evaluated for sensitivity and specificity in extrapulmonary tissues including liver. The Xpert assay can provide a result in 2 hours and has also the benefit of detecting rifampin (RIF) resistance mutations, a marker of multi-drog resistant TB. As newer tests become more available applying faster methods for diagnosing Hepatic TB may promote early detection and prompt initiation on treatment (6) (24)

For these patients starting antituberculous treatment as soon as possible is a must.

Progressive multifocal encephalitis (PML)

Progressive multifocal encephalitis (PML) is a demyelinating central nervous system disease, induced by reactivation of JC virus (DNA virus, Polyomaviridae genus, Papovaviridae family), in patients with severe immunsuppression, is characterized by typical hystological and neuroradiological features. PML prevalence is 0,7-8% among AIDS-defining diseases and it remained unchanged after highly active antiretroviral therapy (HAART) introduction, when compared to other oportunistic infections and to HIV encephalopathy, the incidences of which are nowadays diminished with 50% on HAART. PML lesions are demyelinating (produced through oligodendroglia infection and lysis), usually in multiple foci, in the cerebral white matter. The clinical features are corresponding to the lesions' topography, mainly with motor impairement, like hemiparesis. (9)

Clumsiness may be the first symptom. Hemiparesis is the most common finding. Aphasia, dysarthria, and hemianopia are also common. Multifocal cortical damage produces cognitive impairment in two thirds of patients. Sensory, cerebellar, and brain stem deficits may be present. Headaches and convulsive seizures are rare and occur most often in patients with AIDS. Gradual, relentless progression culminates in death, usually 1 to 9 months after symptoms begin. (11)

Prolonged survival and recovery of neurologic deficits consequent to PML have been seen on rare occasions in association with underlying immunosuppressive conditions other than AIDS, and in patients with AIDS who were treated with triple HAART that included a protease inhibitor. (17)

Antiretroviral treatment and Directly Observed Treatment Short-Course (DOTS)

Antiretroviral therapy and DOTS are formally synergistic, because without undergoing both together, HIV-infected TB patients have a short life expectancy, typically less than five years. (25) Prognosis for HIV-TB co-infected patients has been substantially improved because the simultaneous treatment with ART and DOTS.

The therapeutic results can be also influenced by overlapping toxicity of the two therapies, drug interactions, different degree of drug absorption, and paradoxical reactions. The two main difficulties in combining these drugs derive from potentially severe drug–drug interactions between rifampin and selected ART drugs (particularly the protease inhibitors) and the emergence of the immune reconstitution inflammatory syndrome (IRIS) characterized by a worsening clinical picture or the appearance of new TB lesions. Drug interactions arise because rifampin is a potent inducer of the hepatic cytochrome CYP450 enzyme system that reduces the plasma concentration of coadministered drugs metabolized through this pathway.

The standard WHO recommended antituberculosis regimen is a six month course of rifampicin and isoniazid, with the addition of pyrazinamide, together with ethambutol (or streptomycin) during the first two months of treatment. Supplementation with daily pyridoxine (vitamin B6) to prevent isoniazid induced neuropathy is now routine.

Disease caused by resistant bacteria fails to respond to conventional, first-line treatment. MDR-TB is treatable and curable by using second-line drugs. However second-line treatment options are limited and recommended medicines may not be always available. The extensive chemotherapy required (up to 2 years of treatment) is more costly and can produce severe adverse drug reactions in patients. In some cases, more severe drug resistance can develop. Extensively drug-resistant TB, XDR-TB, is a form of multi-drug resistant tuberculosis that responds to even fewer available medicines, including the most effective second-line anti-TB drugs. (1) Guidelines recommend standard or individualized treatment regimens according to pathogen susceptibility results.

Best therapeutic response is achieved if the TB regimen includes Hydrazide and Rifampicin. If ART includes antiretrovirals that interfere with Rifampicin, if possible, antiretroviral therapy is delayed, if not, Rifabutin can be administered at a dose of 10-20 mg/ kg/day, instead of rifampicin in patients receiving antiretroviral therapy. The continuation phase recommended is a combination of Hydrazide and Ethambutol up to 9 months. Combining ART and DOTS appears to reduce mortality by up to 80% in TB patients in advanced stages of HIV infection. In the pre-HAART period, HIV-infected patients with CD4 counts < 50mm3 had a 7% monthly mortality from any cause. Clinical and immunological benefits of HAART (highly active antiretroviral therapy) occur very quickly after initiation of treatment.

Drug toxicities were minimized with the introduction of new protease inhibitors, integrase inhibitors, and entry inhibitors for the treatment of HIV. Better data on the drug-drug interactions between ARTs and second-line TB drugs are needed in order to minimize drug toxicities for the treatment of MDR-TB and HIV.

In general, antiretroviral therapy is likely to be most effective, not in reducing TB incidence, but in extending the life expectancy of HIV-positive patients successfully treated for TB.

For our patient the mentioned treatment improved appetite and weight gain and decrease hepatospleno-megaly within the first two or three months. Resolution of fever occurred within 3 weeks of initiating treatment. There were not mentioned any major adverse event up until now.

Conclusion

This is an extremely rare and serious case of XDR tuberculosis with atypical extrapulmonary locations in a patient with a severe immunosuppression and neurological complications. It represents a therapeutic challenge, both in terms of antibacillar and antiretroviral treatment and in terms of the neurological treatment and involves cooperation of a multidisciplinary team requiring prolonged admissions in specialized departments of several hospitals in Craiova and Bucharest.

The increasing numbers of co-infected HIV-TB patients require close cooperation between national programs fighting TB and HIV and the development of guidelines for diagnosis and treatment of HIV-TB concomitance to early prevent, diagnose and treat such cases in the future.

Unfortunately, because of the severe immunosuppression and severe neurological impairement, our patient has a very bad prognosis.

All the authors have the same contributions.

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