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Case Report

# Isoniazid-resistant *Mycobacterium kansasii* in an HIV-positive patient, and possible development of immune reconstitution inflammatory syndrome after initiation of highly active antiretroviral therapy: case report

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SUMMARY

Non-tuberculous mycobacteria are rare but important causes of infection in HIV-positive individuals. A 28-year-old HIV-positive male presented with a high fever, non-productive cough, right subcostal pain, splenomegaly, a very low CD4 count, elevated C-reactive protein and erythrocyte sedimentation rate, and a normal white blood cell count. The suspicion of tuberculosis (TB) was very high, and sputum samples were positive for acid-fast bacilli. Standard quadruple anti-TB therapy was initiated, but once culture of the sample revealed *Mycobacterium kansasii*, pyrazinamide was withdrawn. Highly active antiretroviral therapy (HAART) was initiated soon after, consisting of abacavir/lamivudine and efavirenz. The patient's general condition deteriorated 2 weeks after HAART initiation, which could have been due to the development of immune reconstitution inflammatory syndrome (IRIS). The patient recovered and was discharged in good condition. However, the results of resistance testing of the isolated organism arrived after discharge, and showed isoniazid and streptomycin resistance. This is the first case report of *M. kansasii* infection from Serbia and shows the difficulties encountered during the course of treatment.


## 1. Introduction

*Mycobacterium kansasii* belongs to the group of slowly-growing non-tuberculous mycobacteria (NTM) and is an important cause of infection in both HIV-positive and negative individuals.[1] It is the second most common cause of chronic pulmonary disease in HIV-positive individuals, behind *Mycobacterium avium*.[1,2] *M. kansasii* is a ubiquitous organism. It is widespread in water and soil, and tap water is the most common reservoir for this pathogen.[1–3] Although it is more frequently observed in immunocompromised individuals, an increasing incidence of this organism has not been observed in the HIV/AIDS era.[4] Prevalence rates vary among countries worldwide,[5] and in areas of high prevalence of *Mycobacterium tuberculosis*, NTM are often unrecognized and underdiagnosed.[4] In Serbia, this pathogen is rarely mentioned, with very few papers published regarding its identification.[6,7] This is the first case report from this country.

## 2. Case report

A 28-year old, HIV-positive male, with an illness that had started 17 days prior to admission, presented at the outpatient clinic with a high fever (up to 39.5 °C), accompanied by sweating, pain in the left subcostal region, and a non-productive cough. He also complained of generalized bone and joint pain.

On admission, the patient was subfebrile (37.4 °C), tachycardic (heart rate 115/min), eupneic, had an oxygen saturation ($SaO_2$) of 92%, and blood pressure of 125/70 mmHg. Physical examination revealed oral candidiasis. No heart murmurs were observed, lung sounds were clear, and neither hepatosplenomegaly nor abdominal pain was present. His personal history revealed that he had been diagnosed with HIV 3 years ago, but since his CD4 cell count had been repeatedly over 400/μl at diagnosis, highly active antiretroviral therapy (HAART) had been deferred at that time.

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However, he had not attended for regular follow-up for 2 years. He did not report recent travel and had not been in contact with animals.

Once the patient was admitted, an extensive workup was performed. Laboratory findings included a very low CD4 count (57/μl) and elevated erythrocyte sedimentation rate (ESR; 90 mm/h), C-reactive protein (CRP; 673 mg/L), and fibrinogen (6.3 g/L), while his leukocyte count was normal ($7.8 \times 10^9$/l). Chest X-ray and abdominal ultrasound had been performed 7 days before admission, revealing enhanced lung markings, a pronounced right hilus with patchy adhesions of the diaphragmatic pleura, and splenomegaly ($13.5 \times 7.0$ cm). A diagnostic panel including Venereal Disease Research Laboratory (VDRL), Treponema pallidum hemagglutination assay (TPHA), hepatitis B virus surface antigen (HBsAg), and hepatitis C virus antibodies (anti-HCV), as well as the Mantoux tuberculin skin test, was negative.

Initial empirical therapy included trimethoprim–sulfamethoxazole and fluconazole to cover *Pneumocystis jirovecii* pneumonia (PCP) and candidiasis, but due to his radiographic and clinical findings, tuberculosis (TB) was also considered. Indeed, all three sputum samples were positive for acid-fast bacilli. As a result, standard quadruple anti-TB therapy was initiated. After 20 days of therapy, the patient was afebrile and in good general condition, at which point HAART was initiated, consisting of abacavir/lamivudine and efavirenz. Two weeks after HAART initiation, his general condition worsened; his fever spiked again (up to 40 °C), and a chest X-ray revealed progression of the previous findings. HIV PCR detected a viral load of 1270 copies of HIV RNA per milliliter of plasma. The decline in his general condition, as well as the progression of radiographic findings, are hallmarks of immune reconstitution inflammatory syndrome (IRIS), which is observed in patients initiating HAART with a low CD4 count. Mycobacterial infections are often implicated in this phenomenon.[8] However, reports of IRIS with NTM are not common.[8] Finally, sputum cultures revealed *M. kansasii*. Since all strains are naturally resistant to pyrazinamide, this drug was withdrawn from the patient's regimen.

The patient made a full recovery after 2 months of combined therapy, and a total of six control sputum samples were negative. He was discharged in good general condition and continued his therapy as an outpatient. Ten days after discharge, however, the results of microbial susceptibility testing were finalized and delivered, showing resistance to isoniazid and streptomycin. For technical reasons, it was not possible to perform a CD4+ count after his discharge.

## 3. Discussion

*M. kansasii* is considered one of the most virulent NTM, and observational studies have reported variable mortality rates.[9,10] The clinical presentation is similar to that of *M. tuberculosis*,[9–11] with symptoms of fever and cough usually lasting more than 30 days,[10–14] which is considerably longer than in our patient. After initiation of HAART, the deterioration in his general condition could have occurred for several reasons, one of them being IRIS.[14,15] IRIS is most commonly observed in HIV patients and is considered to be a paradoxical reaction after the initiation of HAART due to the restoration of immune function and 'reactivation' of the inflammatory response.[8,15] It is initially characterized by a worsening of the patient's general condition and the progression of chest X-ray findings, followed by a gradual improvement in clinical and laboratory findings, which was the case in the patient presented here.[8,15]

The initiation of HAART in patients with a mycobacterial co-infection can be challenging, particularly in those with very low CD4+ counts. However, it has been established that the early initiation of therapy significantly reduces mortality rates in patients with CD4+ T-cell counts of $<50/mm^3$, although there is an increased risk of IRIS developing,[24] as occurred in the present case. For these reasons, HAART should be initiated early on and also monitored closely.[16,17]

Isoniazid is a first-line agent against *M. kansasii*, together with rifampicin and ethambutol.[18] However, resistance to isoniazid has been reported,[18] with in vitro resistance rates varying between 8% and 25%.[19–21] Taking into account that all isolates are naturally resistant to pyrazinamide,[18] there should be a concern regarding future treatment, since resistance to other recommended agents including rifampicin, clarithromycin, ciprofloxacin, and moxifloxacin has been reported as well, which could lead to the development of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains.[18–21] Current guidelines suggest that *M. kansasii* in HIV-infected patients should be treated with rifampicin, ethambutol, and either isoniazid or clarithromycin for 15–18 months.[17] Trimethoprim–sulfamethoxazole in high doses is an alternative,[18] but the present patient developed a severe allergic reaction to this drug during his stay, and therefore this was not considered as an option. The patient was switched to clarithromycin and is now being followed up.

In conclusion, the resistance of *M. kansasii* to first-line drugs, the erratic clinical course, and the treatment limitations were the challenges faced in this case. It is important to report cases of NTM in the population, in order to obtain the real picture in terms of prevalence of these rare strains, which can present a significant challenge in terms of treatment. Although the patient responded well to therapy, some key principles have to be kept in mind. Prompt implementation of all available diagnostic procedures is vital, so that proper therapy can be given early on. Resistance of mycobacterial organisms to both standard and non-standard anti-TB agents is becoming an issue in medical practice, which is why antimicrobial susceptibility testing is of vital importance. By doing so, the development of multi-resistant strains can be delayed, and the initiation and successful maintenance of HAART and anti-mycobacterial therapy can be achieved.

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