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Autopsy findings of miliary tuberculosis in a renal transplant recipient

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ABSTRACT

Miliary tuberculosis is a lethal form of disseminated tuberculosis (TB), deriving its name from the millet-seed-sized granulomas in multiple organs. As TB still remains a leading cause of morbidity and mortality in India, its disseminated forms need to be diagnosed early to ensure more aggressive treatment at the earliest possible time. However, a considerable number of cases are missed ante-mortem. We discuss the case of a 32-year-old immunocompromised, non-HIV patient with an ante-mortem diagnosis of pulmonary TB. However, multiple organ involvement by *Mycobacterium tuberculosis* was demonstrated on autopsy. This case highlights the role of autopsy as a research and learning tool, and prudential clinico-pathologic correlation, which will improve clinical outcomes in the future.

Keywords

Miliary Tuberculosis; Renal Transplant; Autopsy

INTRODUCTION

Worldwide, tuberculosis (TB) remains one of the leading causes of morbidity and mortality in spite of global control efforts. According to the Global Tuberculosis Report, published in 2015,¹ an estimated 9.6 million people developed TB worldwide and 1.5 million died from the disease. In India, 2.2 million cases were reported that year, making it the country with the highest burden of TB.

Miliary TB is a pathological term, derived from the Latin word "miliarius," meaning related to millet seed, describing millet-seed-sized (1-2 mm) granulomas in various organs affected by the tubercle bacilli. It results from massive lymphohematogenous dissemination from a *Mycobacterium tuberculosis*-laden focus.² This term was coined by John Jacob Manget in 1700.^{2,3} Classically described on a chest x-ray, this pattern of

involvement is seen in 1-3% of all TB cases. However, autopsy studies of adults have documented a higher proportion of patients, accounting for 0.3-13.3% of all autopsies, and 11.9-40.5% of all cases of TB.^{4,5} We present the case of disseminated TB in a non-HIV, immunocompromised individual for the rarity of involvement of nine organs, and stress the importance of pathologic autopsy as a teaching and research tool.

CASE REPORT

The deceased, a 32-year-old male who underwent renal transplant 3 years earlier in the backdrop of bilateral focal segmental glomerular sclerosis, was admitted with complaints of anorexia, marked

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weight loss over the past 2 months, and recent onset dyspnea. He was not on hemodialysis; however, he was on immunosuppressive therapy with tacrolimus and mycophenolate mofetil. Over the previous week, he'd had a productive cough and a high-grade intermittent fever with rigor and chills. His past history was significant with episodes of recurrent hospital admissions over the past 6 months during which he was treated for *Pneumocystis jiroveci* pneumonia, based on clinical suspicion, and a non-healing ulcer over his left elbow. At presentation, he was febrile with no icterus, cyanosis, pedal edema, or lymphadenopathy. On examination of his chest, there were crackles over bilateral lung fields with reduced air entry. However, there were no findings consistent with pleural effusion. His abdominal examination was essentially normal.

Computed tomography of his chest revealed multiple cavitary nodules (4-9 mm) in both lungs (left > right, scattered in all fields). Bronchoscopy with broncho-alveolar lavage fluid revealed the presence of acid/alcohol fast bacilli. The sputum for acid-fast bacillus (AFB) was positive, and the serology for HIV and hepatitis B were negative.

The patient was started on first-line anti-tubercular therapy and antifungal therapy due to clinical suspicion of pulmonary Koch's and recurrent *Pneumocystis jiroveci* pneumonia. His condition failed to improve despite active medical management. His platelet count fell to 34,000/mm³ from 175,000/mm³ (reference value [RV]: 150,000-400,000/mm³) at the time of admission, and his urea and creatinine increased to 89 mg/dL and 2.23 mg/dL, respectively (RV: urea 15-40 mg/dL, creatinine 0.2-1.3 mg/dL). His total leukocyte count rose to 20,000/mm³ (RV: 4,000-11,000/mm³) with a differential count of 94% neutrophils, and a deranged coagulation profile. The patient complained of a dull, aching, continuous pain in the right iliac fossa. On examination, tenderness in that area was noted. Based on clinical findings and supporting laboratory data, a provisional diagnosis of acute on chronic graft rejection was made. An ultrasonography of the abdomen was essentially normal except for a minimal localized collection in the right iliac fossa. However, over the next 2 days, his condition gradually deteriorated, and finally, he succumbed to his illness. We received the body for pathological autopsy to ascertain the cause of death and to establish clinicopathological correlation.

AUTOPSY FINDINGS

After receiving the required consent from the patient's family members, an autopsy was performed. The external examination was unremarkable except for postmortem lividity in dependent areas, and the setting in of rigor mortis. A 3 × 2 cm healing ulcer with no active discharge was present over the left elbow, and a well-healed surgical scar was present in the right iliac region. On examination of the thoracic cavity, both lungs were firm and heavy, with the right and left lung weighing 700 g and 500 g, respectively (RVs: right lung 450 g; left lung 395 g). Numerous small yellow-white-colored nodules were noted throughout both lung parenchyma, predominantly in the left lung. (Figure 1A). Multiple enlarged pre- and para-tracheal lymph nodes were present, and a few of them exuded purulent yellowish material. There was minimal pleural fluid and pericardial cavity, and the heart appeared unremarkable. Bone marrow samples were collected from the sternum.

On examination of the abdominal cavity, there was no free fluid. The liver weighed 1750 g (RV: 1400 g) and had numerous yellow-colored nodules scattered in the parenchyma (Figure 1B).

Similar nodules were seen in the spleen (Figure 2A) while the pancreas appeared normal. Bilateral native kidneys were small and shrunken, and no nodules were seen. However, the transplanted kidney showed similar millet-sized, multiple, yellowish nodules all over the surface (Figure 2B). The cranial cavity examination was unremarkable and cerebrospinal fluid was collected for culture.

There was a 10 cm gangrenous intestinal segment near the ileocecal junction (Figure 3) along with necrotic mesenteric lymph nodes, which exuded purulent material from which a scrape smear for cytology was immediately prepared, and another sample was sent to the microbiology laboratory for culture.

MICROSCOPIC EXAMINATION

Microscopic examination of the sections taken from the nodules seen on the gross examination of both lungs, the liver, spleen, transplanted kidney, and gangrenous intestinal segment, revealed numerous caseating granulomas (Figures 4A-D and 5A). Similar findings were present in the paratracheal lymph nodes and mesenteric nodes (Figure 5B).

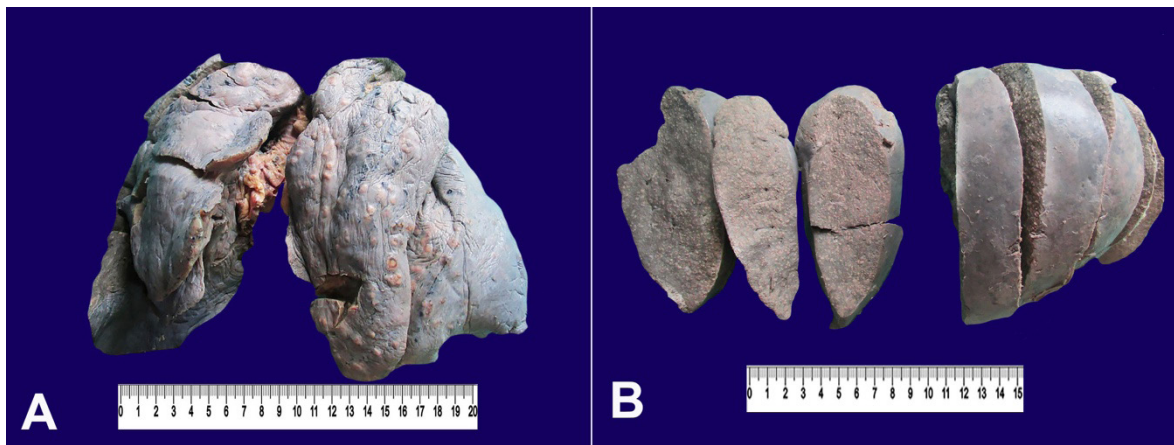


Figure 1. Gross findings of the lungs (A), and the liver (B) showing millet-like nodules observed over the pleural surface and within the hepatic parenchyma.

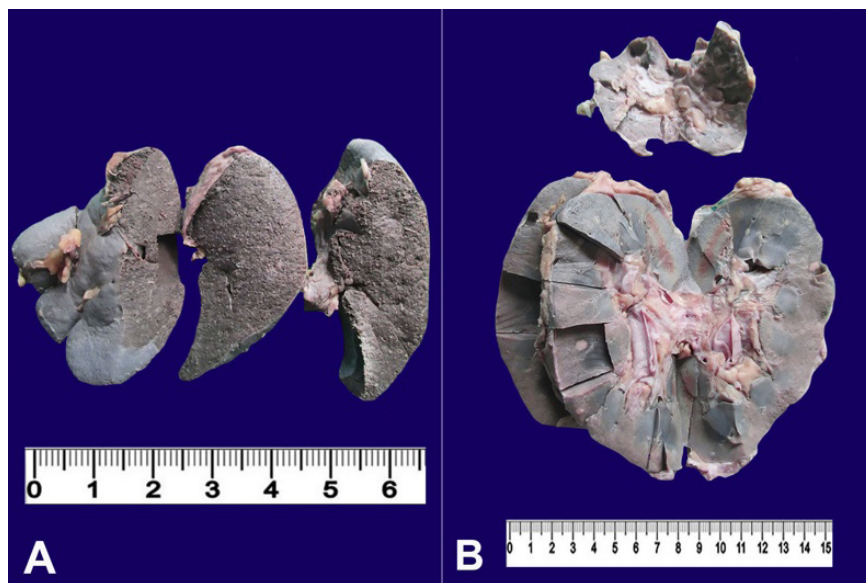


Figure 2. Gross findings of the spleen (A) and the kidneys (B) (native, top image; and transplanted, bottom image) showing several millet-like nodules.

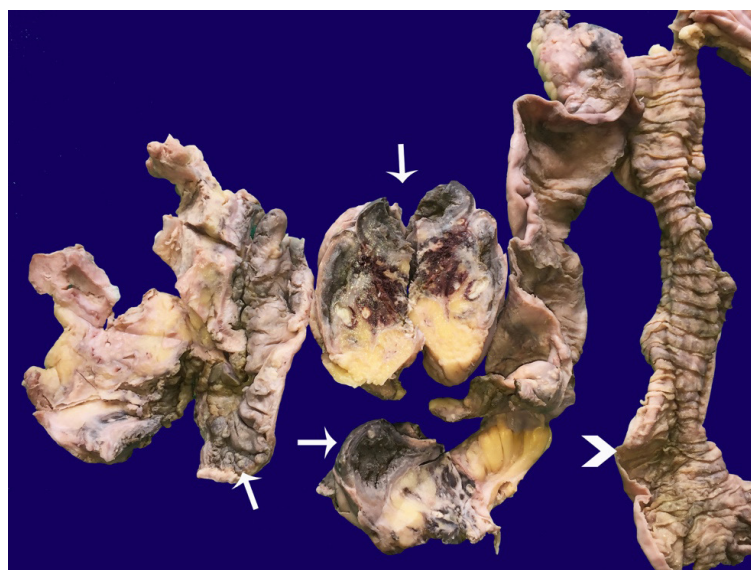


Figure 3. Gross findings of gangrenous ileal segment (arrows) with multiple small yellowish nodules in the mesenteric fat compared to normal intestinal segment (arrowhead).

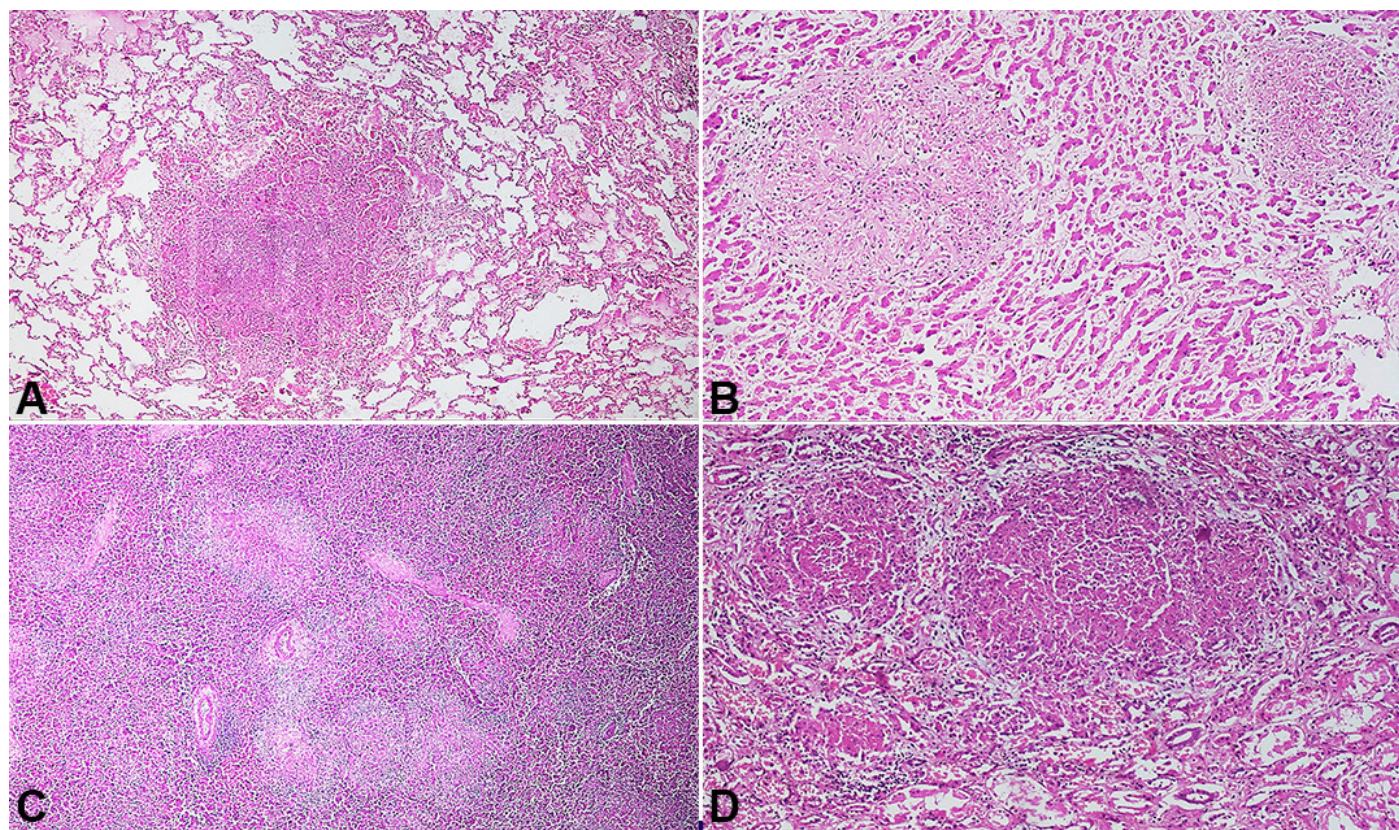


Figure 4. Photomicrography of (A) lung, (B) liver, (C) spleen, and (D) kidney, showing caseating granuloma (H&E, 40X).

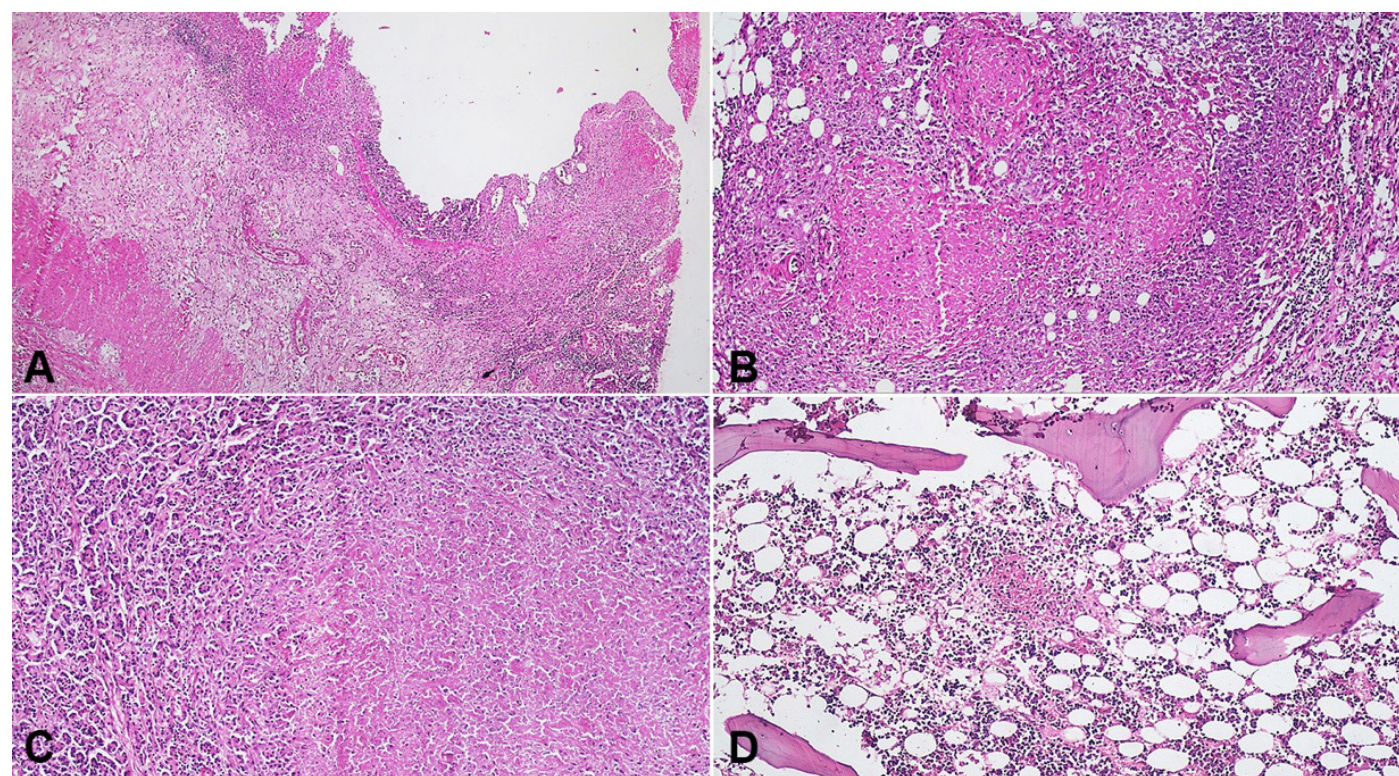


Figure 5. Photomicrography of (A) ileal segment showing necrosis and a caseating granuloma (H&E, 40X); (B) Mesenteric lymph node with granuloma (H&E, 40X); (C) Pancreas with a huge granuloma with caseous necrosis (H&E, 40X); (D) Bone marrow with a granuloma (H&E, 40X).

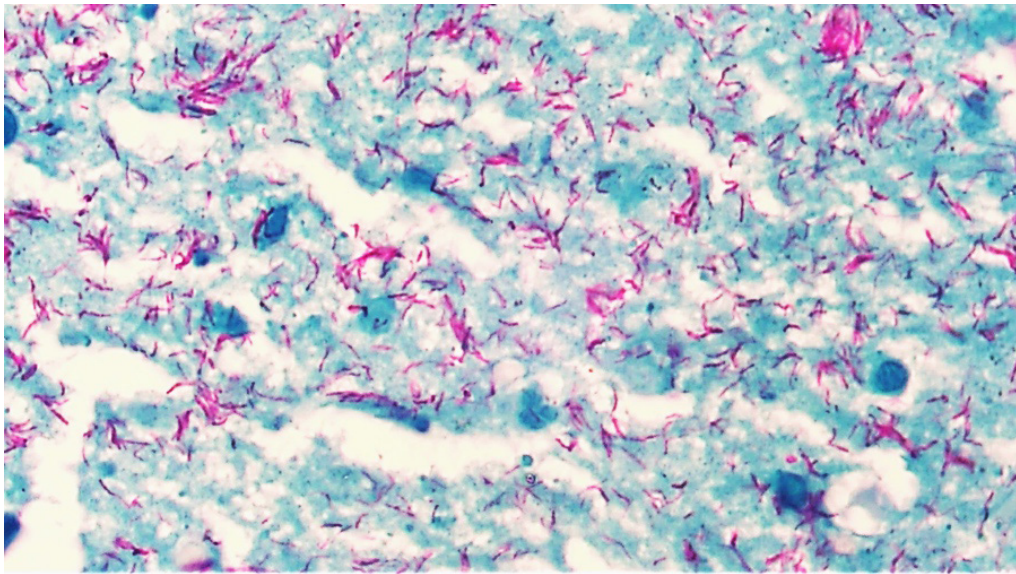


Figure 6. Photomicrography of the mesenteric lymph node showing several acid-fast bacilli (Ziehl-Neelsen, 100X).

In addition, ill-defined granulomas were noted in the grossly normal-appearing pancreas and bone marrow (Figures 5C and 5D). The Ziehl-Neelsen staining demonstrated the AFB in all of these organs, except the bone marrow (Figure 6). AFB were isolated on culture from the purulent exudate collected from the mesenteric nodes.

In the lung, along with the multiple caseating granulomas, the alveoli showed pneumonic consolidation filled with inflammatory infiltrates comprising lymphocytes, histiocytes, and polymorphs. Hemosiderin-laden macrophages were present. There was no evidence of hyaline membrane. Sections from adrenals revealed features of congestion. However, no granulomas were noted.

So, with a clinical suspicion of disseminated TB and supporting laboratory findings, such as (i) deranged renal function tests and coagulation profile; (ii) a fall in haemoglobin and platelets; (iii) a progressively increasing total leukocyte count; and (iv) a demonstration of multiple organ involvement by *Mycobacterium tuberculosis* bacilli on autopsy, the cause of death was attributed to sepsis and multi-organ failure secondary to disseminated progressive primary TB in a renal transplant recipient.

DISCUSSION

Disseminated TB refers to the involvement of more than two organs by *Mycobacterium tuberculosis* with miliary TB being one of its lethal forms. The organs that are most commonly involved (other than the lungs) are

bone marrow, liver, lymph nodes, spleen, pancreas, brain, eye, intestines, genitourinary tract, and skin.

Relatively limited data and varied clinical manifestations make the ante-mortem diagnosis of miliary TB a formidable challenge in most cases, accounting for the high mortality rates among patients.⁴ Ours is one of the few case reports that documents the miliary pattern of multi-organ involvement in an immunocompromised, non-HIV patient. Although a diagnosis of pulmonary TB is generally made ante-mortem, miliary TB may present a clinical course accompanied by a challenging diagnosis. In many such cases, it is difficult to ascertain the correct sequence of events and the actual cause of death. In our case, we favored the hypothesis of the lungs being the primary focus of TB because: (i) the patient's initial complaint was respiratory distress and the pain in the right iliac fossa was referred afterwards; (ii) there was a history of recurrent hospital admissions over the previous 6 months due to respiratory infections; and (iii) the fact that the overall incidence of primary lung focus was much higher than primary ileal TB. Therefore, we considered the infection to have started within the lungs and then spread throughout the body causing multi-organ failure in an immunocompromised patient. However, the possibility of a gangrenous ileal segment as the possible primary focus of the TB and sepsis is still debatable.

Autopsy continues to be a means of establishing the diagnosis of previously undetected cases and confirming the diagnosis in those suspected during life.⁶ On many occasions, causes of death established at autopsy have been shown to differ from those

suspected by clinicians.⁷ Besides a reliable source for confirming or ruling out the diagnoses, autopsy provides valuable information regarding associated diseases that may also play an important role in clinical evolution. As in this case, pain in the right iliac fossa was clinically attributed to a possible acute on chronic graft rejection; however, a gangrenous ileal segment along with purulent mesenteric nodes at the ileocecal junction positive for AFB noted at autopsy correlated with the clinico-pathological diagnosis of disseminated TB. Diagnoses detected at autopsy, which were clinically missed, may have important implications on research and epidemiological data, and a greater clinical implication, as autopsy results provide essential feedback for clinicians in the management of such cases in future. TB is still a major health-related economic burden worldwide, especially in developing countries. Therefore, clinical-pathological correlations are needed in order to understand and manage this disease, and to subsequently enhance clinical performance.

CONCLUSION

Autopsy remains the gold standard, not only in establishing the diagnosis of miliary TB but also as a teaching and research tool, for understanding the pathological intricacies of poorly understood medical pathologies.

The study and publishing of data in this article have the approval of the institutional ethics committee, Armed Forces Medical College, Pune, Maharashtra, India - 411040.

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