Incidental Tuberculosis in sudden, unexpected, or violent deaths in the community Lusaka, Zambia - A descriptive forensic post-mortem examination study

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Title:

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Highlights:

- Forensic autopsies of community deaths show incidental, undiagnosed TB cases
- Undiagnosed TB and related deaths reveal gaps in TB control programs
- TB remains an important public health problem in Lusaka, Zambia
- Low social-economic status and TB are intertwined in these cases

ABSTRACT: (198 words)

Objectives:

Tuberculosis remains a global emergency. In Zambia only 55% of tuberculosis cases are diagnosed. We performed a study to determine incidental cases of tuberculosis seen at forensic autopsy of individuals who died suddenly and unexpectedly in the community in Lusaka, Zambia.

Methods:

Whole-body autopsies were performed according to Standard Operating Procedures. Representative samples obtained from relevant organs were subjected to pathological examination. Information on circumstances surrounding the death was obtained. Data on patient demographics, gross and microscopic pathological findings, and cause(s) of death were analysed.

Results:

Incidental tuberculosis was found in 52 cases (45 male, 7 female, age range 14-66) out of 4286 whole-body autopsies. 41/52 (80%) were aged 21-50 years. One was a 14-year old boy who died during a football match. 39/52 (75%) deaths were attributable specifically to tuberculosis only. Other deaths were due to acute alcohol intoxication(4), violence(7), ruptured ectopic pregnancy(1), bacterial meningitis (1). All the cases were from poor socio-economic backgrounds and lived in high-density areas of Lusaka.

Conclusions:

Incidental cases of active tuberculosis undiagnosed antemortem seen at forensic autopsy reflects major gaps in the national TB control programs. More investments into proactive screening, testing, treatment activities, and accurate data collection are required.

Keywords: Tuberculosis, Autopsy, Forensic, Incidental TB, World TB Day

INTRODUCTION

Community (sudden, unexpected, and violent) deaths have significant medicolegal importance (Inquests Act of 1939; Spitz, 2006). The coroner thus scrutinises these deaths with the aid of the Office of the State Forensic Pathologist (OSFP) to establish the cause and manner of death using forensic procedures (Inquests Act of 1939; National Forensic Act of 2020). Forensic procedures, specifically the forensic autopsy, provides a unique opportunity to study a range of underlying communicable and non-communicable diseases not detected ante-mortem (Mucheleng'anga et al., 2021; Himwaze et al., 2021).

Despite treatment being available, Tuberculosis (TB) remains a global emergency and is the second commonest infectious disease worldwide causing death (WHO, 2021). In 2018, the total burden of TB in Zambia was estimated to be 72 495, and of these, 40 176 (55%) were diagnosed with TB. Of the 36 431 (50%) started on treatment, only 32 700 (45%) completed treatment (Lungu et al., 2021). Forensic autopsy data may thus provide insight into the undiagnosed and sub-clinical burden of clinically undiagnosed TB in the community and who may be succumbing to the disease. Autopsies can also play a critical role in defining cryptic presentations of TB (Rasika & Gilks, 2015). Undetected TB has significant implications as infected individuals may be a source of transmission in the community (Muhammad et al., 2021). However, the burden of undiagnosed TB in community deaths has not been estimated in Lusaka, Zambia.

We performed a case series study of incidental TB cases seen at forensic autopsy of individuals who died suddenly, unexpectedly, or violently in the community in Lusaka, Zambia. We also reviewed literature on tuberculosis findings at autopsy.

MATERIALS AND METHODS

Ethics approval

The coroner gave authority to conduct the forensic autopsies through an Order for Post-mortem Examination of community deaths. Forensic autopsies are mandated by law; thus, no consent or ethical permission is required to conduct the autopsy. Approval was obtained from the OSFP to access this anonymized data. The OSFP granted permission to access autopsy reports (autopsy findings and causes of death) and publish the data (Mucheleng'anga et al., 2021).

Study design

We conducted retrospective case series analyses of whole-body forensic autopsies we had performed on community deaths in Lusaka, Zambia from January 2016 to December 2021 in which TB was an incidental finding or a cause of death. Information on the circumstances surrounding the death, symptoms, and past medical history was obtained from the next of kin by the Forensic Pathologist (FP) or Anatomic Pathologist (AP) as per procedure before the autopsy was conducted and the Coroners Order for Post-Mortem Examination.

Autopsy procedures

Autopsies were performed by either an FP or an AP. Personal Protective Equipment (PPE) was used, including a full gown, plastic apron, gloves (including cut-proof under gloves), face visor, boots, and N95 masks. Autopsies were performed in line with guidelines in the Practice Manual for Medicolegal Death Investigations at the OSFP in Zambia. In all cases, we followed universal precautions using PPE. A double pair of standard disposable surgical latex gloves in addition to cut-resistant gloves were also used (Mucheleng'anga, et al., 2021).

Tissues sampled and histological examination

Representative samples were obtained from the relevant organs as required, submitted in standard tissue cassettes, and fixed in 10% neutral buffered formalin for 72 hours. The samples were processed, embedded in paraffin, sectioned, mounted onto glass slides, and stained using hematoxylin and eosin (H&E) staining according to the Standard Operating Procedure Manual at the UTH histopathology Laboratory. All slides were examined together by the FP and AP (Mucheleng'anga et al., 2021). Slides that revealed granulomatous inflammation were further subjected to Ziehl-Neelsen (ZN) staining techniques to confirm the presence of acid-fast bacilli.

Diagnosis of Tuberculosis

The diagnosis of Pulmonary TB (PTB) was based on autopsy findings of consolidation or cavitation in the apices of the lungs, caseating lesions, histology showing granulomatous inflammation, and confirmation of tubercle bacilli by using ZN stain. Diagnosis of Extra Pulmonary TB (EPTB) was based on caseating lesions, histology showing granulomatous inflammation, and confirmation of tubercle bacilli using ZN stain.

Data collection and analyses

Data on the decedent demographics, history, circumstances, autopsy findings, and opinion of the cause of death was entered in Excel and analysed using STATA version 14. The variables were grouped and presented as frequencies and percentages (Mucheleng'anga, et al., 2021).

Cause(s) of Death Formulation

The cause of death was formulated within the context of the circumstances surrounding the death, history of the case, post-mortem examination findings, and ancillary studies (Mucheleng'anga et al., 2021).

RESULTS

Table 1 summarises the demographics and circumstances decedents. They all died suddenly, unexpectedly, and violently and were brought in dead (BID). There were fifty-two cases with active TB disease of 4286 whole-body autopsies performed. None of them had been detected or suspected ante-mortem. All decedents were from poor social-economic backgrounds and lived in high-density areas of Lusaka.

Forty-five were male, and seven were female, and the age ranged from 14-66 years. There was one paediatric TB death. The age ranges 31-40, 21-30, and 41-50 years were the most common at 20 (38.48%), 12 (23.08%), and 9 (17.31%), respectively. The age ranges 51-60 and 61-70 had 4 cases each at 7.69%, respectively. Three (5.77%) cases were in the age range 11-20.

Thirty-seven (71.15%) cases died at home, while five (9.62%) died enroute to the hospital, with three (5.77%) cases died at the workplace. Seven cases were referred for a forensic autopsy for violent deaths, three (5.77%) for road traffic accidents, and four (7.69%) for assault. One paediatrics TB death involved a 14-year old boy who died suddenly while playing football.

Table 2 summarises the autopsy findings. PTB was the most common finding in 36 (69.23%). "Mesenteric lymph node, splenic, and PTB" were present in 6 (11.5%) of cases. "Mesenteric lymph node hilar lymph node TB" was found in 2 (3.85%) cases. "Abdominal and pelvic TB," "Cardiac and hepatic TB," "Kaposi's' sarcoma and PTB," "Pulmonary, abdominal, and renal TB," "PTB, aspergillosis, bacterial meningitis, neurocysticercosis," "Pulmonary, renal, splenic and hepatic TB," "Pulmonary, TB pericarditis, and Cardiac cysticercosis" and "TB pericarditis" were found at 1 case (1.92%), in each combination respectively. PTB was also found in cases with other sites of involvement in nine (9) cases (17.30%). Mesenteric lymph node involvement was found in 8 (15.35%) cases in cases with other TB sites. Hepatic TB was found in 2 (3.85%) of cases with other TB sites. TB infection of the heart was found in 2 (3.85%) cases.

Table 3 summarises the Cause of Death (CoD) statements. PTB and disseminated TB were the commonest causes of death in 23 (44.23%) and 10 (19.23%) cases, respectively. Acute alcohol intoxication and EPTB were CoDs in 8 cases at 7.69% each. Road traffic accidents caused three

(5.76%) deaths. Blunt impact trauma due to assault, manual strangulation, and pulmonary haemorrhage due to PTB were CoDs in 6 cases at 3.85%, respectively. Two cases had CoDs attributed to ruptured ectopic pregnancy and bacterial meningitis at 1.92%, each.

Gross pathology and microscopic findings

Figure 1 shows representative gross pathology and microscopic pathology images.

Gross pathology:

The image in **figure 1 A** shows an apical cavity with whitish central caseation. The image in **figure 1 B** shows hilar lymphadenopathy with a firm consistency and grey colour. **Figure 1 C** depicts Miliary pulmonary and splenic disease, with individual lesions that are small, firm (2-mm) foci of white consolidation scattered through the lung and spleen parenchyma. The images in **figure 1 D** depicts TB pericarditis with pericardial thickening caused by fibrin and collagen formation.

Micrographs:

The micrograph in **Figure 1 E** shows a necrotic area that appears as a structureless collection of fragmented cells and amorphous granular debris within a distinctive inflammatory border in the lung parenchyma. **Figure 1 F** shows a necrotic area that appears as a structureless collection of lysed cells and amorphous granular debris within a distinctive border within the kidney parenchyma.

DISCUSSION

There are several notable findings from this series. First, the majority of TB deaths occurred at home or in community settings. Second, forensic autopsies of community deaths can reveal undetected TB. Third, forty-seven of the fifty-two cases showed pulmonary disease. Fourth, PTB was a definitive cause of death in thirty-six cases and a contributing cause in eleven others. Fifth, all fifty-two cases of decedents with TB seen at autopsy were not suspected of having TB prior to death and the diagnosis was only apparent on autopsy.

Tuberculosis is the second most common cause of death from infectious diseases worldwide (WHO, Fact sheets 2021). In sub-Saharan Africa, poor economic and social factors together with suboptimal performance of national TB programs due to lack of resources required to proactively screen, find and treat all cases of TB, continue to drive the TB epidemic (WHO, Fact sheets 2021). In 2019, the incidence rate of TB was 333 per 100 000 per year in Zambia, with 15 400 TB-related deaths (Lungu, et al., 2021).

Several studies conducted worldwide have shown TB at forensic autopsies. A study from India showed a 5.1% rate of TB at forensic autopsies. An ante-mortem diagnosis was not made in 84.6% (Punia, et al., 2012). Another study from Turkey reported a 1 % TB rate among forensic autopsies (Ozsoy, et al., 2010). A study in New Zealand identified TB as a cause of death in 0.2% of autopsies done (Lum & Koelmeyer, 2005). In Cape Town, South Africa, a study revealed a TB prevalence of 6.2% in persons with sudden unexpected death (Muhammad, et al., 2021). The variation in the prevalence of TB cases identified at forensic autopsy may allude to regional differences in the prevalence of the infection.

Undiagnosed tuberculosis identified at forensic autopsy is not uncommon since TB is a chronic disease and take several weeks or months to manifest clinically (Rastogi et al., 2011). Previous autopsy studies from Zambia showed an undiagnosed case load of TB in adults and children inpatients (Chintu, et al., 2002; Bates, et al., 2015; Bates, et al., 2016).

This case series shows decedents at autopsy without suspicion of having TB prior to death. Their demographics, circumstances of death, co-infections, and the extent of the disease have been highlighted. All the cases in the series were of poor social-economic status and lived in high-density areas of Lusaka. A high proportion of low socio-economic status individuals live in overcrowded households, which directly fosters TB transmission (WHO, 2021). We postulate that groups from high-density and poor social-economic status areas, household contacts of those with infectious TB,

and contacts known to be HIV positive must be targeted for screening given that Lusaka high-density areas are also known to have high HIV prevalence (Pelissari, et al., 2017).

Forty-one of fifty-two cases were in the age range 21-50 years, with the 31-40 range contributing most cases. This finding contrasts with a study in Germany which showed that most of the cases were within the age ranges of 30-59 and 80-99 (Theegarten, et al., 2006) The difference is related to the differences in HIV prevalence and the social-economic status of the countries. The difference may also be attributed to differences in the age structure of the two populations (Mucheleng'anga, et al., 2021). However, our results are similar to a study in a forensic population by Himwaze et al., 2020 in Lusaka, who found similar results and concluded that this age group was most at risk of premature death due to increased alcohol intake and outdoor activities in the forensic population (Himwaze, et al., 2020). There were more males than females in our series. This is consistent with our previous autopsy studies (Mucheleng'anga, et al., 2021; Himwaze, et al., 2020). It has been suggested that males are more predisposed to sudden, unexpected, and violent deaths due to complications of disease arising from poor health-seeking habits (Himwaze, et al., 2020).

Regarding the circumstances surrounding the death, many sudden and unexpected deaths occurred outside the hospital facility, either at home, at work, or on the way to the health facility in the series. These circumstances again emphasize the hypothesis that this predominantly male population dies suddenly and unexpectedly outside the health facility due to complications of disease arising from poor health-seeking habits (Mucheleng'anga, et al., 2021; Himwaze, et al., 2020). An autopsy study in South Africa revealed a high proportion of pulmonary TB in people who died at home without an apparent cause of death. This was attributed to the high burden of HIV infection (Omar, et al., 2015). Himwaze, et al., 2020, found an HIV prevalence of 31% in the forensic population at autopsy in Lusaka (Himwaze, et al., 2020). The forensic population is known to suffer from advanced disease due to the self-rationalisation of symptoms and a failure to seek medical attention (Spitz, 2006; Mucheleng'anga et al., 2021). The one paediatric TB death involved a 14-year-old boy who died suddenly during a football match. This is a telling example where TB kills "silently." At autopsy, a

TB pancarditis was diagnosed. The screening of TB contacts for individuals who are both symptomatic and asymptomatic, often neglected, can be an essential benefit to the community of individual children. This child would have benefited from TB treatment if screening had been conducted (Omar, et al., 2015).

Pulmonary TB (apical cavitation, consolidation, granulomatous inflammation), was our series' most common autopsy finding. These were confirmed on histology and confirmed by positive ZN staining. We observe that the spleen and mesenteric lymph nodes were the second and third most common sites of infection in this series. Three cases had coinfections, the first with aspergillosis, bacterial meningitis and neurocysticercosis. The second with Kaposi's sarcoma and HIV, while the third with TB pericarditis and cardiac cysticercosis.

TB was the primary cause of death in thirty-nine of fifty-two incidental TB cases of TB seen at autopsy, with Pulmonary (23 cases) and disseminated (10 cases) being the commonest CoD, respectively. Four cases had pulmonary TB but died of acute alcohol intoxication. Seven cases were violent deaths but revealed TB on autopsy. Evidence of undiagnosed TB suggests that TB-related mortality is under-ascertained and under reported. There is therefore need for more research into active screening methods in the community as autopsies provide the most accurate data about cause of death despite being operationally difficult and expensive .We postulate that more TB cases could be found by searching more actively among specific population groups (Omar, et al., 2015).

Diagnosis of incidental TB in community deaths reflects the burden of disease within the community and while public health efforts worldwide are being directed towards reducing the spread of TB, the forensic autopsy is a vital tool in detecting unknown TB cases in the community (Mucheleng'anga, et al., 2021). Forensic autopsy data are thus indispensable for disease intelligence and prevention and may be helpful and lead to timely medical intervention for the decedent's relatives who might have been exposed to TB. These data can help public health map disease surveillance systems, implement

public awareness programs for prevention, and treat sources in households and the community (Rasika & Gilks, 2015; Dye, et al., 2006; Syed, et al., 2015).

There have been previous calls to conduct forensic autopsy studies in community deaths to identify undiagnosed TB cases (Syed, et al., 2015). The actual data on the causes of deaths in the community (rural and urban) and in hospitals in most SSA countries remain unknown, and the quality of cause-specific mortality statistics remains poor. Thus, there is an urgent need to obtain more accurate cause-of-death data from SSA countries by reviving routine autopsies which declined in most SSA countries because of several reasons, such as lack of resources to maintain an effective pathology service, scarcity of trained pathologists, inadequate infrastructure, and difficulties in obtaining consent for autopsies due to cultural beliefs and religious sensitivities (Chintu, et al., 2002). This case series is one such activity related to that clarion call.

Our data should be viewed under the limitations of the study. This case series is limited by the small number of cases because not all violent deaths such suicides and road traffic accidents undergo a whole body autopsy, possibly leading to missed incidental TB. Additionally culture and polymerase chain reaction testing was not done. ZN staining that was used to confirm the presence of tubercle bacilli in tissue at autopsy does not distinguish tuberculous from non-tuberculous mycobacterial infections. Future autopsy studies should include mycobacterial culture and molecular analyses for more accurate diagnosis of *Mycobacterium tuberculosis* (*Mtb*) in autopsy tissues.

Our autopsy study serves as a pivotal starting point for conversations around future autopsy studies in the SSA focused on TB pathology, pathogenesis and co-infections. Undiagnosed TB cases and other co-morbidities such as HIV, malaria, COVID-19, hypertension, diabetes, and other diseases require further investigation. Our previous COVID-19 autopsy studies in Zambia have highlighted the need for sequencing data to align to autopsy studies (Mucheleng'anga, et al., 2021; Himwaze et al., 2021). Apart from more investments into TB programs, for more proactive screening, testing and treatment activities, accurate data collection, revamping autopsy studies worldwide would provide more insights

into the actual mortality burden. *Mtb* can persist intracellularly in lung tissue without histological evidence of tuberculous lesions (Hernandez-Pando et al, 2000), and autopsy studies provide opportunities to study latent TB infection, early TB disease not manifest clinically and host-*Mtb* interactions.

Conflicts of interest: All authors declare no conflict of interest.

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Author contributions:

Luchenga Mucheleng'anga and Alimuddin Zumla ideated the study and contributed equally. Luchenga Adam Mucheleng'anga, Viktor Telendiy and Cordilia Maria Himwaze performed the forensic autopsy investigations. Amos Hamukale analysed the data. All authors contributed to intellectual discussions and manuscript writing.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Luchenga Adam Mucheleng'anga, Viktor Telendiy and Cordilia Maria Himwaze performed the forensic autopsy investigations. Luchenga Mucheleng'anga, Cordilia Maria Himwaze and Alimuddin Zumla ideated the study and contributed equally. Amos Hamukale analysed the data. All authors contributed to intellectual discussions and manuscript writing.

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LEGENDS TO TABLES AND FIGURES

LEGENDS TO TABLES

Table 1
Decedent's demographics, circumstances of death

Table 2
Sites of Tuberculosis at autopsy

Table 3
Autopsy Cause(s) of Death

LEGENDS TO FIGURES

Figure A: Secondary tuberculous-apical cavitation in lung

Figure B: Tuberculous hilar lymphadenopathy

Figure C: Miliary tuberculous in Lung (Left) and Spleen (Right)

Figure D: Fibrinous tuberculous pericarditis

Figure E: Caseating granuloma in lung (Micrograph at x 4 magnification)

Figure F : Caseating granuloma in kidney (Micrograph at magnification x 10)

Table 1: Decedent's demographics, circumstances of death

	Frequency	Percent	Cum.
Age in Years			
11-20	3	5.77	5.77
21-30	12	23.08	28.85
31-40	20	38.46	67.31
41-50	9	17.31	84.62
51-60	4	7.69	92.31
61-70	4	7.69	100
Sex			
Female	7	13.5	13.5
Male	45	86.5	100
Circumstances of Death			
Assaulted	4	7.69	7.69
Road Traffic Accident	3	5.77	13.46
Sudden Unexpected Death at Home	37	71.15	84.62
Sudden Unexpected Death at Work	3	5.77	90.38
Sudden Unexpected Death on Way to Hospital	5	9.62	100

Table 2: Organs affected by Tuberculosis at Autopsy

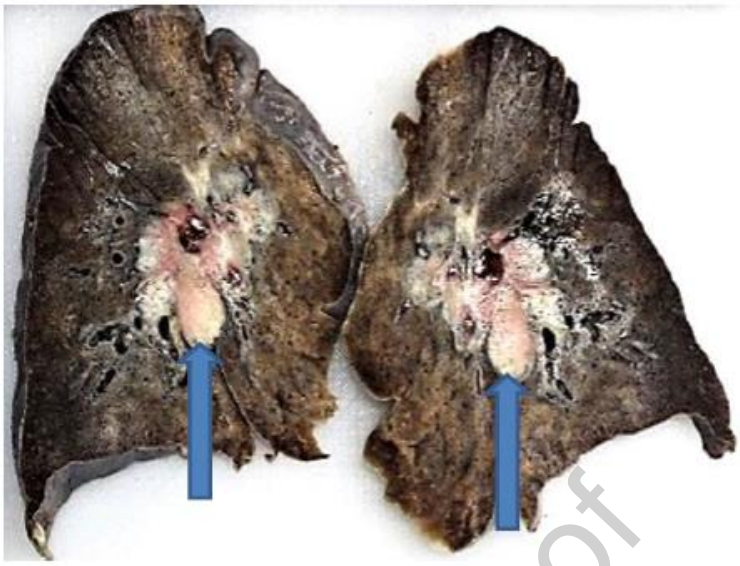
	Frequency	Percent	Cum.
Abdominal and pelvic TB	1	1.92	1.92
Cardiac and hepatic TB	1	1.92	3.85
Kaposi's sarcoma and Pulmonary TB	1	1.92	5.77
Mesenteric and Hilar lymph node TB	2	3.85	9.62
Mesenteric lymph node, Splenic and Pulmonary TB	6	11.5	19.23
Pulmonary TB	36	69.23	88.46
Pulmonary, Abdominal and Renal TB	1	1.92	90.38
Pulmonary TB, Pulmonary aspergillosis, Bacterial Meningitis, Neurocysticercosis	1	1.92	92.31
Pulmonary, Renal, Splenic and Hepatic TB	1	1.92	94.23
Pulmonary and TB Pericarditis, Cardiac cysticercosis	1	1.92	98.08
TB Pancarditis	1	1.92	100.00

Table 3: Autopsy Cause(s) of Death

	Frequency	Percent	Cum.
Acute Alcohol Intoxication	4	7.69	7.69
Blunt Impact trauma to head due to Assault	2	3.85	11.54
Blunt impact trauma to the head due to RTA	3	5.76	17.31
Disseminated TB	10	19.23	36.54
Ruptured Ectopic pregnancy	1	1.92	38.46
Extrapulmonary TB	4	7.69	46.15
Manual Strangulation	2	3.85	50.00
Bacterial Meningitis	1	1.92	51.92
Pulmonary TB	23	44.23	96.15
Pulmonary haemorrhage due to Pulmonary TB	2	3.85	100.00

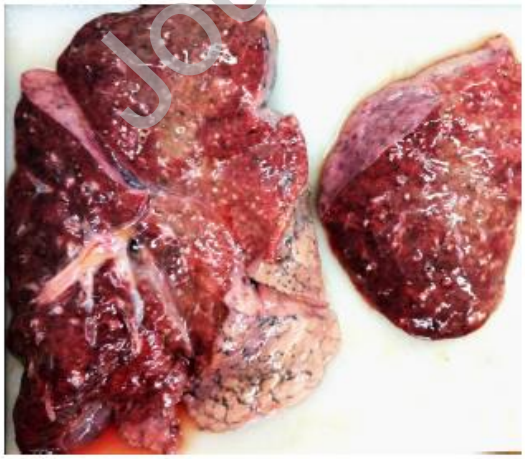
A. Secondary Tuberculous-apical cavitation in Lung

B. Tuberculous hilar lymphadenopathy

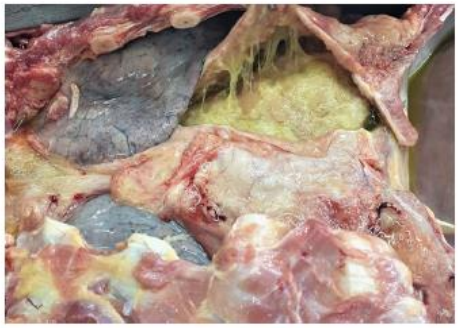


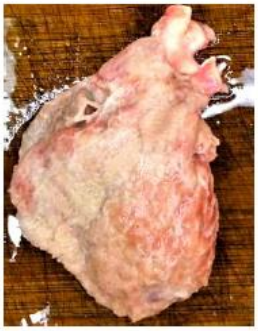
C. Miliary tuberculosis

Lung **Spleen**



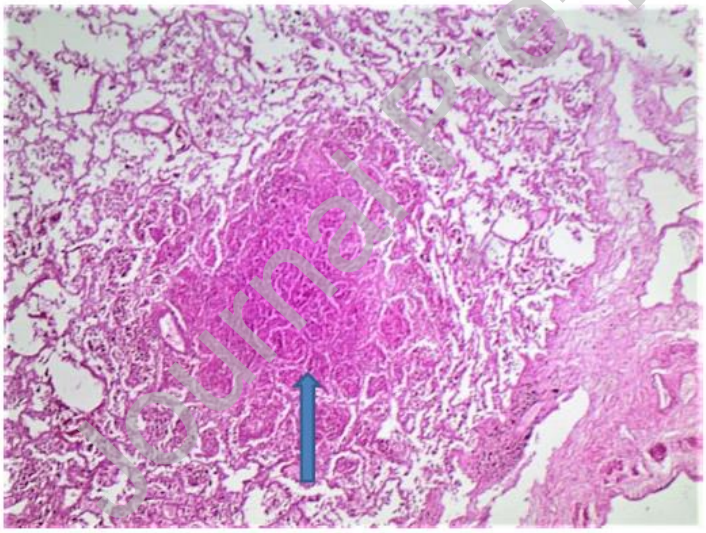
D. Fibrinous Tuberculous pericarditis





E . Caseating granuloma in lung

Micrograph at x 4 magnification:



F. Caseating granuloma in kidney

Micrograph at magnification x 10: