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### Aims and Scope

Asian Archives of Pathology (AAP) is an open access, peer-reviewed journal. The journal was first published in 2002 under the Thai name “วารสารราชวิทยาลัยพยาธิแห่งประเทศไทย” and English name “Journal of the Royal College of Pathologists of Thailand”. The journal is a publication for workers in all disciplines of pathology and forensic medicine. In the first 3 years (volumes), the journal was published every 4 months. Until 2005, the journal has changed its name to be “Asian Archives of Pathology: The Official Journal of the Royal College of Pathologists of Thailand”, published quarterly to expand the collaboration among people in the fields of pathology and forensic medicine in the Asia-Pacific regions and the Western countries.

The full articles of the journal are appeared in either Thai or English. However, the abstracts of all Thai articles are published in both Thai and English languages. The journal features letters to the editor, original articles, review articles, case reports, case illustrations, and technical notes. Diagnostic and research areas covered consist of (1) **Anatomical Pathology** (including cellular pathology, cytopathology, haematopathology, histopathology, immunopathology, and surgical pathology); (2) **Clinical Pathology (Laboratory Medicine)** [including blood banking and transfusion medicine, clinical chemistry (chemical pathology or clinical biochemistry), clinical immunology, clinical microbiology, clinical toxicology, cytogenetics, parasitology, and point-of-care testing]; (3) **Forensic Medicine (Legal Medicine or Medical Jurisprudence)** (including forensic science and forensic pathology); (4) **Molecular Medicine** (including molecular genetics, molecular oncology, and molecular pathology); (5) **Pathobiology**; and (6) **Pathophysiology**.

All issues of our journal have been printed in hard copy since the beginning. Around the late 2014, we developed our website ([www.asianarchpath.com](http://www.asianarchpath.com)) in order to increase our visibility. We would like to acknowledge that our journal has been sponsored by the Royal College of Pathologists of Thailand. We have the policy to disseminate the verified scientific knowledge to the public on a non-profit basis. Hence, we have not charged the authors whose manuscripts have been submitted or accepted for publication in our journal.

On the other hand, if any authors request a printed copy of the journal issue containing the articles, each of the copied journals costs 450 bahts for Thai authors and 30 United States dollars (USD) for international authors.

### Publication Frequency

Four issues per year

## **Disclaimer**

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**ORIGINAL ARTICLE**

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# Incidence of Pulmonary Tuberculosis among Decedents Underwent Autopsy at Institute of Forensic Medicine

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## Abstract

**Background:** Tuberculosis (TB) remains a formidable threat to global public health, causing significant morbidity and mortality. In 2021, TB claimed the lives of 1.6 million individuals worldwide, making it the second leading cause of infectious disease mortality, after COVID-19. Healthcare workers and forensic staff are at heightened risk of contracting TB.

**Aim:** The objective of this study was to investigate the incident of pulmonary TB cases among individuals who underwent forensic autopsy at the Institute of Forensic Medicine.

**Materials and Methods:** A retrospective search was conducted on autopsy records from July to September 2022, with a review of histological slides of the lungs. Suspected cases were subjected to confirmatory testing for the presence of TB.

**Results:** Of the 1,282 autopsied cases during the three-month study period, 15 were identified as having pulmonary TB. Of these, 12 were confirmed to have died from or had suspected pulmonary TB as the cause of death.

**Conclusion:** Healthcare workers and forensic staff are at high risk for TB infection, particularly in the autopsy room. Early detection and management of TB cases are crucial in reducing transmission and minimizing the risk of infection.

**Keywords:** Autopsy, Forensic, Tuberculosis

## Introduction

Pulmonary tuberculosis (TB) is a highly infectious and potentially fatal disease caused by *Mycobacterium tuberculosis*. According to the World Health Organization (WHO), TB is one of the leading causes of death worldwide, responsible for an estimated 1.4 million deaths in 2019 (WHO, 2020). In Thailand, TB is a significant public health problem, with an incidence rate of 129 cases per 100,000 people in 2019 (WHO, 2021)<sup>(1)</sup>.

Personnel working in medical and forensic departments are at a high risk of exposure to TB, especially during autopsies. The autopsy room is a particularly high-risk environment due to the generation of respiratory secretions and aerosols during the procedure, which may contain high concentrations of TB bacteria<sup>(2)</sup>. This poses a significant risk to the health and well-being of personnel in these departments, as well as to the wider public health.

A study by Baussano et al.<sup>(3)</sup> highlights the risk of TB among healthcare workers, particularly those working in high-risk settings such as the autopsy room. The study identified healthcare workers as being at a higher risk of TB infection compared to the general population due to their frequent exposure to infected patients. The study also highlighted the need for increased awareness and screening for TB among healthcare workers to prevent the transmission of the disease.

Another study by Uden et al.<sup>(4)</sup> reviewed the risk of TB infection and disease for healthcare workers and found that the risk varied depending on the type of healthcare worker and their level of exposure. The study highlighted the importance of implementing effective infection control measures in healthcare settings to prevent the transmission of TB.

In addition to healthcare workers, forensic personnel are also at risk of TB exposure, especially during autopsies. The risk of TB transmission in the forensic department is of particular concern due to the potential for contamination of the autopsy environment and the exposure of personnel to high concentrations of TB bacteria. A review by Fares et al.<sup>(5)</sup> identified the risk of TB exposure in the forensic department and highlighted the need for effective infection control measures to be implemented to prevent the transmission of the disease.

The forensic implications of TB were also discussed in a study by Iseman and Madsen.<sup>(6)</sup> The study highlighted the potential for TB to be used as a bioweapon and the importance of early detection and treatment of the disease. The study also discussed the potential for TB to be used as a tool for forensic investigation, with TB strains being used to identify the geographical origin of an individual.

Given the high risk of TB exposure in the forensic department, it is important to determine the incidence rate of TB in individuals who have undergone autopsy. This information can be used to develop effective strategies to mitigate the risks associated with TB exposure in the autopsy room and to prevent the transmission of the disease.

To determine the incidence rate of pulmonary TB in individuals who have undergone autopsy at the Institute of Forensic Medicine in Thailand, a retrospective study was conducted from July to September 2022. The study reviewed real cases that were autopsied at the Institute of Forensic Medicine during this period.

## **Materials and Methods**

A retrospective analysis was conducted on cases that underwent whole-body autopsy at the Institute of Forensic Medicine, Bangkok, Thailand between July and September 2022. The autopsies were conducted in accordance with the institute's usual standard. Cases that did not undergo a full autopsy and therefore could not provide a lung sample for histopathological investigation, such as those with extensive decomposition, skeletonization, or other factors precluding the collection of lung samples, were excluded from the study. A total of 1,282 cases were included in the study.

The pathology of lungs in each case was reviewed using both gross examination and histopathological examination with hematoxylin and eosin (H&E) staining, according to standard practice. If slides revealed granulomatous inflammation or there was suspicion of pulmonary TB infection, Ziehl-Neelsen (ZN) staining techniques were used to confirm the presence of acid-fast bacilli.

The diagnosis of pulmonary TB was based on gross autopsy findings such as consolidation, caseating lesions, histology showing granulomatous inflammation, and confirmation of the presence of acid-fast bacilli using ZN stain.

After diagnosis, cases with pulmonary TB infection were identified, and demographic data, clinical history, cause of death, and all relevant information were reviewed and recorded for analysis and reporting purposes.

## **Results**

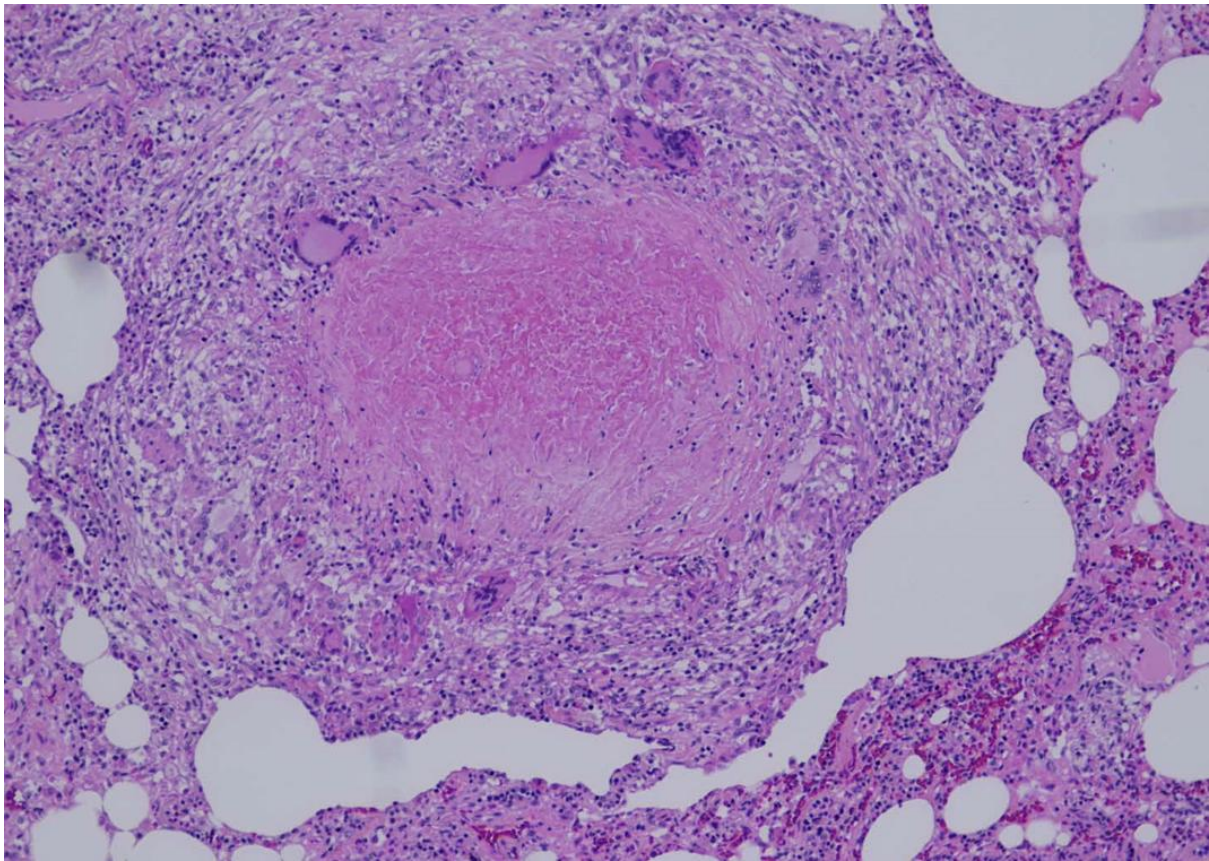
Between July and September 2022, 15 out of 1,282 autopsy cases were diagnosed with pulmonary tuberculosis (PTB). The age range of the individuals was between 35 to 70 years. Among the 15 cases, 12 were men and 3 were women. Majority of the cases were Thai nationality (12 cases), whereas, the others were Laotian, Myanmarese, and unidentified nationalities. Most of the cases were from Bangkok (13 cases), while the other two cases were from Samut Prakan. (Table 1)

**Table 1** All 15 cases diagnosed with pulmonary TB infection and their demographic data

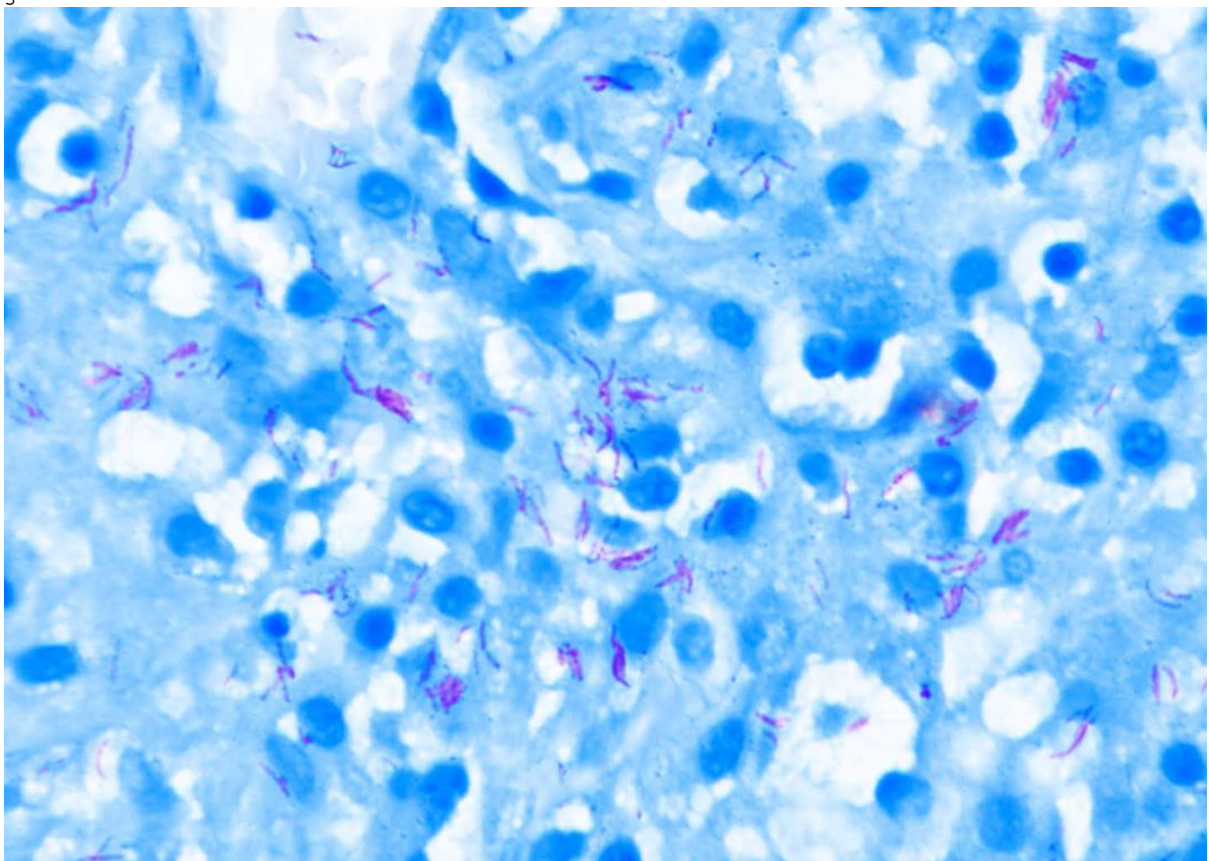
No.	Month	Age	Nationality	City	Gender	Cause of death	Granulomatous Inflammation in H&E	AFB stain
1.	July	47	Thai	Bangkok	male	MI with TB infection	yes	positive
2.	July	40	Thai	Bangkok	male	pneumonia sepsis	yes	negative
3.	July	46	Laos	Bangkok	female	pneumonia	yes	positive
4.	July	69	Thai	Bangkok	male	pulmonary TB	yes	positive
5.	July	70	Thai	Bangkok	female	undetermined suspected from pulmonary pathology	yes	positive
6.	August	~40	undetermined	Bangkok	male	pulmonary TB	yes	positive
7.	August	58	Thai	Bangkok	male	pneumonia	yes	positive
8.	August	66	Thai	Bangkok	male	MI	yes	positive
9.	August	60	Thai	Samut Prakan	male	pulmonary TB	yes	positive
10.	August	65	Thai	Samut Prakan	male	pneumonia with pulmonary TB infection	no	positive
11.	August	63	Thai	Bangkok	male	pneumonia with pulmonary TB infection	yes	positive
12.	August	54	Thai	Bangkok	male	pneumonia	yes	negative
13.	September	50	Thai	Bangkok	male	undetermined	yes	positive
14.	September	59	Thai	Bangkok	female	SAH from TA	yes	positive
15.	September	35	Myanmar	Bangkok	male	disseminated tb	yes	positive

Out of the 15 cases, 12 were confirmed to have pulmonary TB and were diagnosed as the cause of death, while in the remaining 3 cases, two were declared to have died due to myocardial infarction (MI) and one was diagnosed with subdural hemorrhage from a traffic accident as the cause of death.

The diagnosis of pulmonary TB was established by combining gross pathology findings at the autopsy room, histopathology of lung tissue with granulomatous inflammation, and the detection of acid-fast bacilli using Ziehl-Neelsen (ZN) staining. Among the 15 cases, 14 showed lung pathology on Hematoxylin and Eosin (H&E) staining (Figure 1), while 13 showed the presence of tubercle bacilli on ZN staining. (Figure 2) The two cases with negative ZN stain results may be due to different stages of TB infection or previous treatment of the infection<sup>(7)</sup>.



**Figure 1:** H&E stain (magnification x10) of central caseation surrounded by epithelioid and multinucleated giant cells



**Figure 2:** Zeihl-Neelsen stains (magnification x100) for acid-fast bacilli

## Discussion

Tuberculosis (TB) is a highly infectious disease caused by the bacterium *Mycobacterium tuberculosis*. It primarily affects the lungs, but can also affect other parts of the body, such as the brain, bones, and kidneys. TB is transmitted from person to person through the air when someone with TB coughs, sneezes, or talks, and another person inhales the bacteria. Healthcare workers (HCWs) are at increased risk of contacting TB due to their close contact to patients with the disease. This risk is further compounded by factors such as poor ventilation and inadequate infection control measures in healthcare settings.

A study conducted in the Amhara Region of Ethiopia reported a high prevalence of active TB disease among HCWs and support staff in healthcare settings<sup>(8)</sup>. The study found that 5.3% of HCWs and 2.3% of support staff were diagnosed with active TB disease. The study also revealed that the risk of contacting TB was higher among HCWs who had been working in healthcare settings for more than 5 years. This finding highlights the importance of regular screening and early detection of TB among HCWs to prevent the spread of the disease.

Another study conducted in Thailand reported a surprising incidence of TB among a new generation of highly exposed HCWs who may be asymptomatic<sup>(9)</sup>. The study found that 14% of HCWs who were exposed to TB patients at a university hospital were diagnosed with latent TB infection (LTBI). Of these HCWs, 40% were asymptomatic and were only detected through routine screening. The study highlights the need for regular screening and early detection of LTBI among HCWs, even if they are asymptomatic.

A study conducted at Chiang Mai University Hospital in Thailand reported the clinical characteristics, drug resistance, and treatment outcomes of TB disease among HCWs<sup>(10)</sup>. The study found that the majority of HCWs with TB disease had pulmonary TB and were diagnosed through routine screening. The study also found that a significant proportion of HCWs with TB disease had drug-resistant TB, which can be more difficult to treat. The study highlights the importance of regular screening and early detection of TB among HCWs, as well as the need for effective TB treatment regimens that have drug resistance patterns.

A study conducted in Zambia investigated the prevalence of incidental TB in sudden, unexpected, and violent deaths in the community<sup>(11)</sup>. The study found that 3.3% of deaths were attributed to TB, and that many of these deaths were not previously diagnosed with TB. The study highlights the need for increased awareness of TB among healthcare providers and the public, as well as the importance of early detection and treatment of TB to prevent unnecessary deaths.

An older study from 2006 investigated the exposure and protection of HCWs to *Mycobacterium tuberculosis* at autopsy<sup>(12)</sup>. The study found that HCWs who performed autopsies on patients with TB were at increased risk of exposure to the bacterium, but that the risk could be reduced using appropriate protective measures such as personal protective equipment and improved ventilation. The study highlights the importance of implementing

appropriate infection control measures in healthcare settings to protect HCWs from exposure to TB.

This study aimed to determine the incidence rate of pulmonary tuberculosis (PTB) in individuals who have undergone autopsy in the Institute of Forensic Medicine in Thailand. The study found that 15 out of 1,282 autopsy cases were diagnosed with PTB, resulting in an incidence rate of 1.17%. The results of this study have important implications for infection control measures in forensic departments, particularly during autopsies.

The results of this study also highlight the need for healthcare workers, particularly those working in high-risk settings such as the autopsy room, to undergo regular screening for TB. Healthcare workers are at a higher risk of TB infection due to their frequent exposure to infected patients. Early detection and treatment of the disease are crucial in preventing the transmission of TB.

One limitation of this study is that it is a retrospective analysis of cases that underwent autopsy at a single institute in Thailand. The results may not be generalizable to other institutes or countries. A larger study with a more diverse population and from multiple institutes is needed to confirm the findings of this study.

Another limitation is that this study only examined individuals who underwent a full autopsy and were able to provide a lung sample for histopathological examination. Cases that did not undergo a full autopsy, such as those with extensive decomposition or skeletonization, were excluded from the study. As a result, the incidence rate of PTB in this study may be an underestimate of the actual incidence rate.

Furthermore, this study did not examine the risk of TB transmission to personnel in the autopsy room. Future studies should investigate the effectiveness of infection control measures in preventing the transmission of TB among personnel in forensic departments

## **Conclusion**

This study shows an incidence rate of 1.17% of PTB in individuals who have undergone autopsy in the Institute of Forensic Medicine in Thailand. The results of this study have important implications for infection control measures in forensic departments, particularly during autopsies. Healthcare workers, particularly those working in high-risk settings such as the autopsy room, should undergo regular screening for TB to prevent the transmission of the disease. Further studies are needed to confirm the findings of this study and investigate the effectiveness of infection control measures in preventing the transmission of TB among personnel in forensic departments.

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**ORIGINAL ARTICLE**

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# Revisiting testicular germ cell tumors according to the 2016 WHO classification

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## Abstract

**Background:** The World Health Organization (WHO) classification of testicular germ cell tumors (TGCTs) has evolved over the years and in 2016 it was restructured. The precursor lesion of TGCTs was termed 'carcinoma in situ' and was later called 'intratubular germ cell neoplasia, unclassified'. These terms were replaced by the term 'germ cell neoplasia in situ' (GCNIS) in 2016.

**Objective:** There are few studies in literature regarding categorization of TGCTs based on the 2016 WHO classification.

**Methods:** This study was conducted over eight years. Approval from the Institutional Ethics Committee was obtained. Histopathological material was examined, and the tumors were classified accordingly.

**Results:** In a period of 8 years, 73 testicular tumors were diagnosed as TGCTs. All were related to GCNIS. We studied a total of 68 cases. Of these, 37 (55%) were of one histological type and 31 (45%) were of mixed histological type. The most common combination of tumors was that of Embryonal carcinoma + Teratoma + Yolk Sac Tumor + Choriocarcinoma. One case had a primitive neuroectodermal component.

**Conclusion:** The 2016 WHO classification is a lucid method of dividing TGCTs according to their pathogenetic mechanism.

**Keywords:** germ cell neoplasia in situ, testicular, tumor, World Health Organization

## Introduction

Testicular germ cell tumors (TGCTs) are strikingly heterogenous, reflecting a complex tumour model and posing serious challenges for pathologists. More than 90% of testicular neoplasms originate from germ cells. One approach at classification of TGCTs is to divide them into three clinical, epidemiological, and histological groups based on age: pre-pubertal, post-pubertal and spermatocytic seminoma<sup>(1)</sup>. This has been adopted in part in the latest working classification. A simpler classification was to divide all TGCTs into seminomas and non-seminomas<sup>(2)</sup>. This is an archaic method of classification and is no longer used. The 2016 World Health Organization (WHO) classification divides TGCTs based on their relation to germ cell neoplasia in situ (GCNIS)<sup>(3)</sup>. This classification is based on the cell of origin. Those neoplasms that are related to GCNIS are then classified into seminomas and non-seminomas. The non-seminomatous tumors include embryonal carcinomas, yolk sac tumors, post-pubertal, teratomas, post-pubertal and choriocarcinomas. These can appear in true forms or mixed. Neoplasms that are unrelated to GCNIS include spermatocytic tumor, yolk sac tumor, pre-pubertal and teratoma, pre-pubertal. These may also be mixed.

Formerly called carcinoma in situ (CIS), testicular intraepithelial neoplasia (TIN) and intratubular germ cell neoplasia, unclassified (IGCNU), GCNIS is a term that has come to formation after years of disagreement and discussion. GCNIS cells are derivatives of primordial germ cells/ gonocytes that failed to metamorphose into spermatogonia. They are frequently found adjacent to invasive tumor foci in 85 – 90% of cases and in ~5% contralateral testis.<sup>(5)</sup> This can be visualized by light microscopy by applying morphologic criteria<sup>(4)</sup>

## Materials and Methods

This study was conducted retrospectively at a medical college attached to a tertiary care hospital in Southern India over an eight-year period (2012 to 2019). Male patients of all ages who had consulted in the surgery outpatient department and who had received a diagnosis on histopathological examination of a TGCT during the period of the study were included in the study. Where histopathological material was unattainable, cases were excluded.

Patients who were diagnosed with TGCTs were chosen by using keywords used to facilitate the search such as 'teratoma', 'embryonal', 'seminoma', 'yolk' and 'mixed germ'. Clinical particulars were obtained by searching through the system of laboratory information and the medical record. From the archives of the department of pathology, the slides stained with hematoxylin and eosin along with the corresponding paraffin blocks that matched the patients were gathered. The histopathology slides were examined, and the cases were then classified according to the classification of testicular germ cell tumors given in the 2016 WHO classification of tumors of the urinary tract and male genital organs.

## Ethical Clearance

Ethical clearance was received before commencement of the study by the Institutional Ethics Committee of Kasturba Medical College, Manipal, Karnataka, India (IEC no. 682/2019).

## Results

In a period of eight years, 249 testicular tumors were diagnosed in our institute of which 73 were diagnosed as testicular germ cell tumors (TGCTs). Of the 73 TGCTs, 29 were seminomas, 35 were mixed germ cell tumors (MGCTs), five were embryonal carcinomas, three were teratomas and one was a yolk sac tumor (YST). Out of the 73 cases, paraffin blocks were not available for five cases therefore the total number of cases recruited in our study was 68. We did not encounter spermatocytic tumors, pre-pubertal tumors, somatic type malignancies or burn-out tumors. In the present study, there were three benign tumors (5%) and 65 malignant tumors (95%). Most of the malignant tumors were MGCT (46%), followed by seminoma (43%). Embryonal carcinoma constituted 6% of the cases, teratoma constituted 4% of cases and YST constituted 1% of the cases. (Table 1)

**Table 1.** DISTRIBUTION OF CASES

DIAGNOSIS	NO OF CASES (n=68)	%
Seminoma	29	43
MGCT	31	46
Embryonal carcinoma	4	6
Teratoma	3	4
Yolk sac tumor	1	1

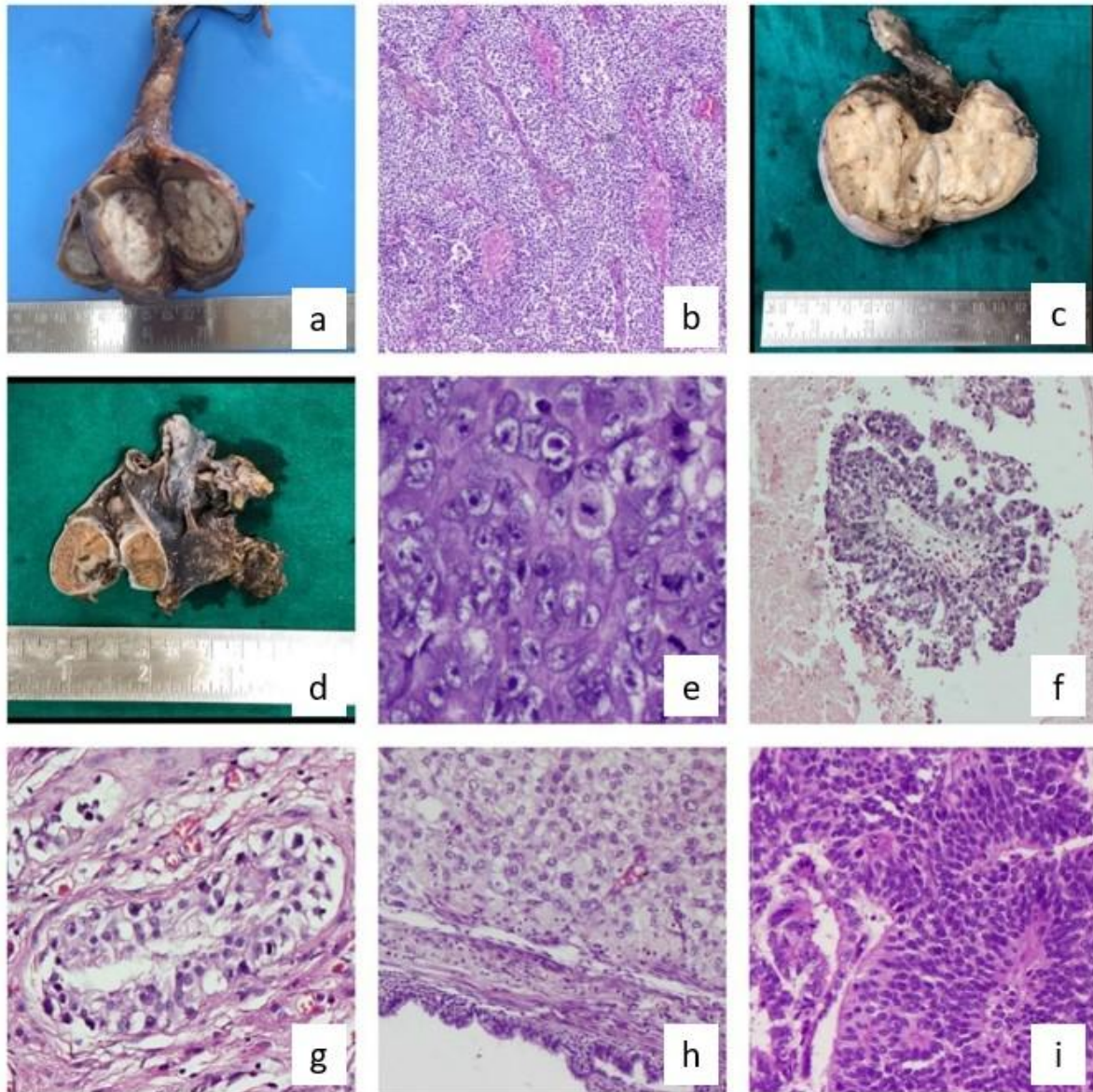
On histologic typing of the 68 cases according to the 2016 WHO classification, a predominance of germ cell tumors was seen. Of the 68 cases, 37 (55%) were germ cell tumors of one histological type including 29 cases of classical seminoma, four cases of embryonal carcinoma, three cases of teratoma, one case of YST and 31 (45%) were testicular germ cell tumors of mixed histological type. The most common combinations of tumors were that of embryonal carcinoma + mature teratoma + YST + choriocarcinoma and seminoma + embryonal carcinoma. The next most common combinations were that of seminoma + immature teratoma + YST, seminoma + mature teratoma, embryonal carcinoma + mature teratoma + YST, embryonal carcinoma + immature teratoma and YST, embryonal carcinoma + immature teratoma, mature teratoma + YST and embryonal carcinoma + YST. There was 1 case each of seminoma + choriocarcinoma + YST, seminoma + choriocarcinoma + embryonal carcinoma + mature teratoma + YST, seminoma + choriocarcinoma + mature teratoma + YST, seminoma + embryonal carcinoma + YST, seminoma + YST, choriocarcinoma + embryonal carcinoma + mature teratoma, YST + immature teratoma + choriocarcinoma and YST + mature teratoma and choriocarcinoma. One case (embryonal carcinoma + immature teratoma) had a primitive neuroectodermal component. (Fig 1, Table 2)

**Table 2.** CLASSIFICATION OF CASES ACCORDING TO 2016 WHO CLASSIFICATION

CLASSIFICATION	NO OF CASES	%
<b>Germ cell tumors</b>	69	100%
<b>Tumors of one histologic type</b>	37	55%
Seminoma	29	42%
Embryonal carcinoma	4	6%
Teratoma	3	5%
YST	1	2%
<b>Tumors of more than one histologic type</b>	31	45%
Seminoma, Choriocarcinoma, YST	1	1%
Seminoma, Embryonal carcinoma, YST, Choriocarcinoma, Mature teratoma	1	1%
Seminoma, Choriocarcinoma, YST, Mature teratoma	1	1%
Seminoma, Embryonal carcinoma, YST, Mature teratoma	3	4%
Seminoma, Embryonal carcinoma, YST	1	1
Seminoma, Embryonal carcinoma	3	9
Seminoma, YST, Immature teratoma	2	2.89
Seminoma, YST	1	1
Seminoma, Mature teratoma	2	2.89
Embryonal carcinoma, YST, Choriocarcinoma, Mature teratoma	3	4
Embryonal carcinoma, YST, Mature teratoma	2	2.89
Embryonal carcinoma, Choriocarcinoma, Mature teratoma	1	1
Embryonal carcinoma, YST, Immature teratoma	2	2.89
Embryonal carcinoma, Immature teratoma	2	2.89
Embryonal carcinoma, Immature teratoma (PNET)	1	1
Embryonal carcinoma, YST	2	2.89
Mature teratoma, YST	2	2.89
YST, Immature Teratoma, Choriocarcinoma	1	1
YST, Mature Teratoma, Choriocarcinoma	1	1

**Table 3.** COMPARISON OF TUMOR DISTRIBUTION WITH VARIOUS STUDIES

TUMOR TYPE	Naqvi S(616) 2006 (n=57)	Deore KS(619) 2015 (n=15)	Chakrabart y PR(620) 2016 (n=37)	Reddy H(618) 2016 (n=14)	Sanjay M(621) 2016 (n=18)	Gupta A(622) 2016 (n=50)	Sharma M(612) 2017 (n=4)	Present study (n=68)
<b>Seminoma</b>	47.4%	26.67%	35.14%	42.9%	38.9%	48%	25%	43%
<b>MGCT</b>	-	33.33%	32.43%	43%	33.33%	16%	25%	46%
<b>Embryonal ca</b>	35%	-	-	7.2%	-	16%	-	6%
<b>Teratoma</b>	8.8%	13.33%	2.7%	-	11.11%	12%	25%	4%
<b>YST</b>	8.8%	6.67%	2.7%	-	5.55%	4%	25%	1%
<b>Others</b>	-	20%	27%	7.2%	11.11%	4%	-	-



**Figure 1:** a. gross image of cut section of a seminoma, b. histology of seminoma (H&E, 10x), c. gross image of cut section of a mixed germ cell tumor, d. gross image of cut section of a pure embryonal carcinoma, e. histology of embryonal carcinoma with mitoses (H&E, 40x), f. histology of a yolk sac tumor showing a Shiller-Duval body (H&E, 10x), g. histology of a seminiferous tubule showing germ cell neoplasia in situ (H&E, 40x), h. histology showing mature teratoma with yolk sac tumor (H&E, 40x), i. mature teratoma showing a primitive neuroectodermal component (H&E, 40x).

## Discussion

In a study conducted by Sharma et al, all testicular tumors studied were germ cell tumors (100%)<sup>(6)</sup>. Dutta et al. reported 90% germ cell tumors in their study with the majority of tumors being MGCTs (33%) followed by seminomas (25%)<sup>(7)</sup>. These findings mirror the findings of our study. Abdulkadir et al found majority of cases in their study to be seminomas (66.7%)<sup>(8)</sup>. Gill et al (36.5% seminomas)<sup>(9)</sup>, Quaiser et al (37% seminomas)<sup>(10)</sup>, Zhang et al (45.5% seminomas)<sup>(11)</sup>, and several other studies reported seminomas as the predominant histologic type of TGCT. These findings do not correlate with the findings of our study. This may be due to the small sample size in our study. The table below compares the distribution of the tumor types within various studies. (Table 3) The findings of Reddy et al are similar to ours<sup>(12)</sup>.

Pugh and Parkinson reviewed various classification of germ cell tumors<sup>(13)</sup>. There existed a 'dual theory' that placed origins of seminomas in intratubular germ cells where non-seminomas originated in blastema displaced early during embryonal life<sup>(14)</sup>. In contrast, the theory that both seminomas and non-seminomas are derived from germ cells as widely accepted. This 'germ cell theory' described the difference in histogenesis of seminomas and non-seminomatous tumors and the passage of non-seminomatous tumors through embryonal carcinoma during differentiation<sup>(15)</sup>.

This was controversial and contested by many histopathologists. Friedmann and Moore were the first to devise a comprehensive classification of TGCTs by proposing four subdivisions of 96% of all testicular tumors. These are the germinoma or seminoma, the embryonal carcinoma with subgroups of teratoma, teratocarcinoma and choriocarcinoma<sup>(16)</sup>. They were the first to call embryonal carcinoma a distinct entity as many workers had previously grouped it seminoma. A modified version of the classification by Dixon and Moore divides TGCTs into five categories: seminoma, embryonal carcinoma, teratoma, teratoma with embryonal carcinoma, and choriocarcinoma<sup>(17)</sup>. (Fig 2)

Albeit convenient for reporting, this was regarded as highly erroneous for histologic classification. Oncologists and andrologists did not favor this classification, deeming it too complex and gave the responsibility to the World Health Organization (WHO) of simplifying it. In 1973, Mostofi and Price led the WHO team of experts and proposed a new classification in which TGCTs were divided into two distinct morphological categories: tumors consisting of one cell type and tumors consisting of more than one type of cell<sup>(18)</sup>.

Dr. Robert E Scully, who was one of the prolific figures in 20<sup>th</sup> century pathology contributed to the classification of premalignant lesions of the testis. The presence of atypical germ cells between germ cell tumors and seminiferous tubules was not unknown and was observed by several famed pathologists by the end of the century. In general, the presence of these cells was believed to be an effect of tumor, or a representation of tumor spread. Azzopardi et al stated that "the significance [of these abnormal intratubular germ cells] could

not be established”.<sup>(19)</sup> In 1972, Skakkebaek coined the term ‘carcinoma in situ’(CIS)<sup>(20)</sup>. This called for revision of the germ cell theory. Prospective studies conducted on infertile men proved the presence of CIS not only in seminomas but also in teratomas, embryonal carcinomas and teratocarcinomas with yolk sac elements. This substantiates the common precursor cell origin of these tumors<sup>(21)</sup>. In 1980 Copenhagen, the first international CIS workshop was co-edited by Dr. Kenneth Grigor, a pathologist from United Kingdom and Jakob Visfeldt<sup>(22)</sup>. Grigor attempted to change the classification of TGCTs to reflect their histogenesis and biology. He recommended the term ‘gonocytoma in situ’ as an alternative to CIS. As the the biological connection proposed by Skakkebaek between fetal gonocytes and post-pubertal germ cell tumors was still considered a controversial one, this proposal, however interesting was not accepted by the wider community<sup>(23)</sup>.

The term CIS had been widely accepted by pathologists in America and Northern European countries as the antecedent lesion to post-pubertal invasive TGCTs. A meeting was held in Minnesota in the year 1980 where esteemed pathologists including Dr. Robert Scully, Dr. Juan Rosai, Dr. F.K.K. Mostofi, Dr. Robert Kurman, Dr. Lucien Nochomovitz and Dr. Edie Heyderman discussed various aspects of testicular tumors. It was agreed upon that the term CIS was a “less than optimal choice” to describe the lesions, as there were no features of epithelial differentiation. Here, Scully recommended the term “intratubular germ cell neoplasia”<sup>(24)</sup>. They proposed another term “intratubular germ cell neoplasia, unclassified” (IGCNU) as it was associated with all morphological types of TGCT, except for spermatocytic seminoma. IGCNU was later adopted by the 2004 WHO classification and placed in many textbooks<sup>(25)</sup>.

A third term, “testicular intra-epithelial neoplasia” (TIN)<sup>(26,27)</sup>, has been used largely in Germany, with it’s continued usage in some centres even today<sup>(28)</sup>.

Spanning the next 30 years, there was a lack of consensus on the terminology which underlined the dissatisfactory nature of these terms. This pre-invasive lesion was neither considered a carcinoma nor “intraepithelial”, as Sertoli cells are not derived from epithelium. The term IGCNU avoided confusion with epithelial-derived neoplasms, however it wrongly implied “unclassified” as an indication of unclear diagnosis or natural history of the neoplasm. The lesion arises in the spermatogonial niche: the area between the tight junctions between the Sertoli cells and the basement membrane forming a ring-like appearance. Later, the pre-neoplastic cells “spill out” in to the lumen of the seminiferous tubule. The “U” in “unclassified” is also sometimes misinterpreted as “undefined”, “unspecific”, “undifferentiated” and “unspecified”. Therefore, there was no resolution on the terms on an international scale, with continued usage of all three terms.

The WHO Classification of genitourinary pathology panel meant for publication in 2016 was to meet, and find some clarification on this issue. It would include several pathologists from many countries, who continued to use the terms CIS and/ or TIN. Initial drafts was to see

a compromise between terms, resulting in “IGCNU/CIS” which appeared unwieldy. This term was seen as unsatisfactory by the testis subset of the panel. At this juncture, Dr. Looijenga<sup>24</sup> suggested “taking ‘germ cell neoplasia” or “germ cell tumour” as a root, and adding “in situ” to either of these terms. Hence, the term “germ cell neoplasia in situ” (GCNIS) took birth, and was unanimously agreed upon.

There are numerous benefits associated with term GCNIS. Firstly, it avoided the epithelial implications related with the term “CIS”. Secondly, it avoided using the confusion associated with the letter “U” and thirdly, the term “in situ” referred to the specific region where TGCTs arise – the spermatogonial niche<sup>(23)</sup>. The result is a classification which is believed to be a better and more terminologically accurate one than any of the predecessors.

Valid reasons exist for these changes. Spermatocytic tumors are not associated with GCNIS or any other germ cell tumor and do not carry the 12p amplification. Instead, they show a unique amplification of chromosome 9. Pre-pubertal yolk sac tumors and teratomas are not associated with GCNIS and do not carry the 12p amplification. Pre-pubertal teratomas do not show any genetic abnormalities, pre-pubertal yolk sac tumors show gains and losses in chromosomal regions that differ from tumors derived from GCNIS.<sup>30</sup> There are no morphological differences between pre-pubertal and post-pubertal yolk sac tumors. There are few differences between pre-pubertal and post-pubertal teratomas. The latter do not show cytological atypia, have a more organoid pattern, show conspicuous squamous and ciliated epithelium along with smooth muscle.<sup>(31)</sup> Both pre-pubertal teratomas and yolk sac tumors behave less aggressively in contrast to their post-pubertal counterparts.<sup>(31-32)</sup> Additionally, under the heading of pre-pubertal teratomas, specialized forms such as dermoid cyst, epidermoid cyst, and carcinoid tumor (well differentiated neuroendocrine tumor) have been placed. This has been validated by the lack of GCNIS and amplification of 12p in the first two entities and most carcinoid tumors, however contradictory reports suggest a dual differentiation pathogenesis for the latter.<sup>(33-35)</sup> Further research into the matter is required.

## **Conclusion**

There are a few limitations in this study. We present a relatively small sample size which restricts the validity of our results. We have included biopsy specimens in our study and therefore do not have access to the gross details of those specimens. Nevertheless, the current 2016 WHO classification divides testicular tumours into those derived from GCNIS derived and those that are not and we have done the same with the tumors detected in this study. This system is pathogenesis-based and revises previous classifications which grouped together morphologically similar but very distinct tumour entities under the same categories.

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## CASE REPORT

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# Metastatic angiosarcoma to the bone marrow: a rare entity

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### Abstract

We report on a rare case of metastatic angiosarcoma to the bone marrow with the liver and spleen suspected as the primary site. The patient was a 68-year-old man who presented with fatigue and later developed signs of liver failure. Enhanced CT scans showed hepatosplenomegaly with multiple hypovascular masses in the liver and spleen. A bone marrow biopsy showed neoplastic spindle-cells with vascular luminal formation and expression of CD31, CD34, ERG and FLI1, consistent with angiosarcoma. Hepatic or splenic angiosarcoma often have metastasis but metastasis to the bone marrow is rare in English literature.

**Keywords:** Angiosarcoma, metastatic angiosarcoma, bone marrow metastasis, hepatic angiosarcoma, splenic angiosarcoma

## Introduction

Angiosarcoma is a malignant vascular tumor which accounts for a small proportion of the vascular tumor category, or approximately 1% of all sarcomas<sup>(1,2)</sup>. The tumor is classified based on primary site and pathophysiology. The tumor usually occurs in the elderly and has a poor prognosis with five-year survival rates of 30%-40%. Clinical manifestations vary based on the subtype and histologic patterns, which may require immunohistochemical staining for diagnosis<sup>(1-3)</sup>. Hepatic or splenic angiosarcomas are a rare subtype of angiosarcoma, but they are also the most common sarcoma in their respective organ<sup>(4)</sup>. Metastasis is common in both subtypes, but metastasis to the bone marrow is rare with a small number of reported cases. Thus, we report on a patient presenting signs of liver failure and further investigations showing metastatic angiosarcoma to the bone marrow. Clinical findings and investigations suspected either the liver or spleen as the primary site. Unfortunately, the patient died before the primary site could be determined.

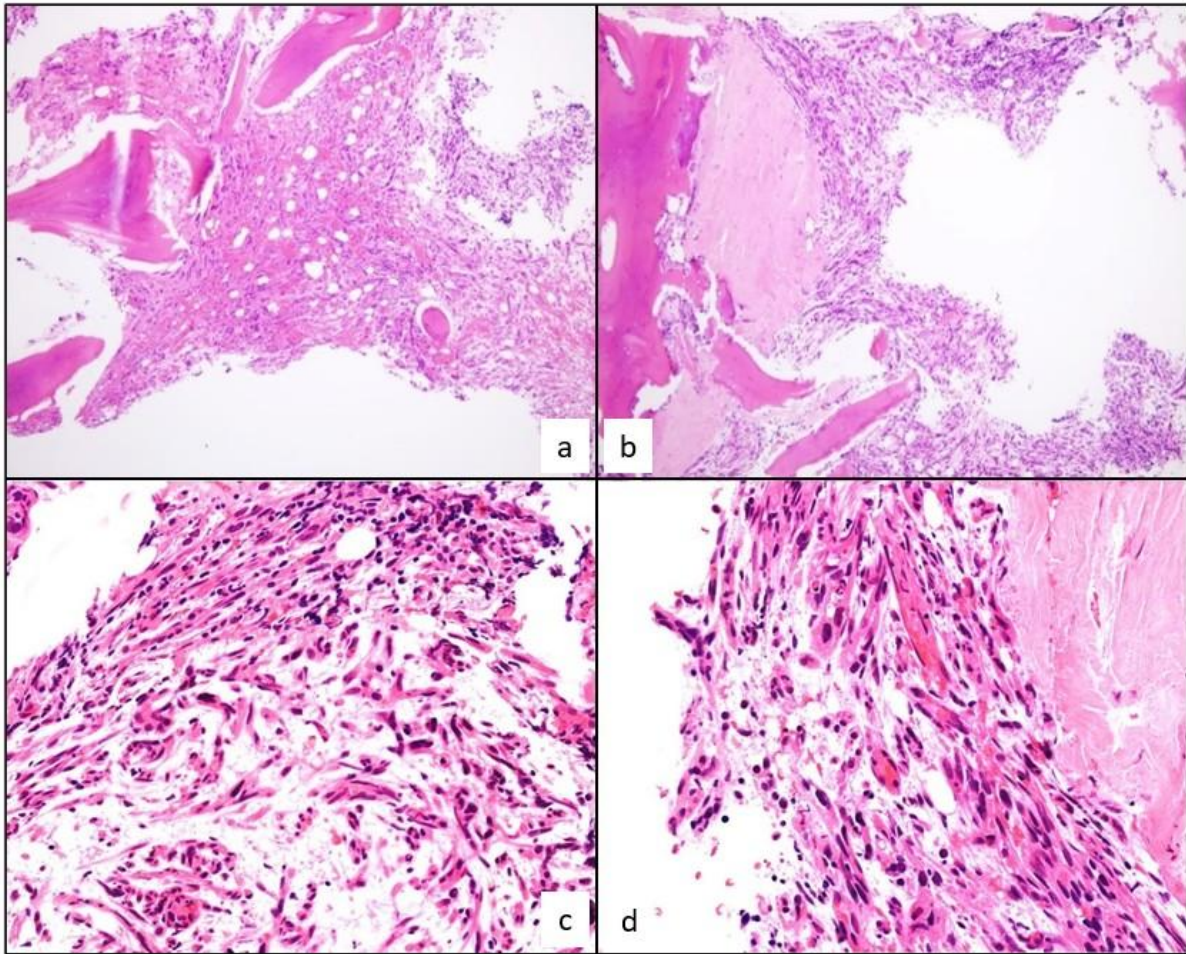
## Clinical information

A 68-year-old man with type 2 diabetes mellitus and hypertension complaint of progressive fatigue for three weeks. He had trouble standing up and walking. He had also lost 2 kg of weight during this period. He denied headache, dizziness, focal weakness, and cognitive or memory impairment. A physical examination revealed broad-based gait without any other neurological deficit. Laboratory findings also showed mild anemia, a positive direct Coomb's test, hyperbilirubinemia and increased liver enzymes. The results were interpreted as consistent with a hemolytic process. A computed tomography (CT) scan of the brain showed only an old lacunar infarct at the left internal capsule without any space-occupying lesion. He was referred for further investigations at another hospital due to a medical coverage issue. The patient was referred back two weeks later and underwent CT scan of chest and whole abdomen, revealing hepatosplenomegaly with multiple hypoenhancing hepatic and splenic masses. In addition, there were multiple osteolytic lesions in the manubrium, sternum, ribs, and vertebrae (Figure 1). He also developed signs of liver failure including ascites, jaundice and flapping tremors. The results of a liver function test were as follows: AST 200 U/L, ALT 41 U/L, ALP 176 U/L and LDH 914 U/L and total bilirubin/ direct bilirubin 6.48/4.6 mg/dl.

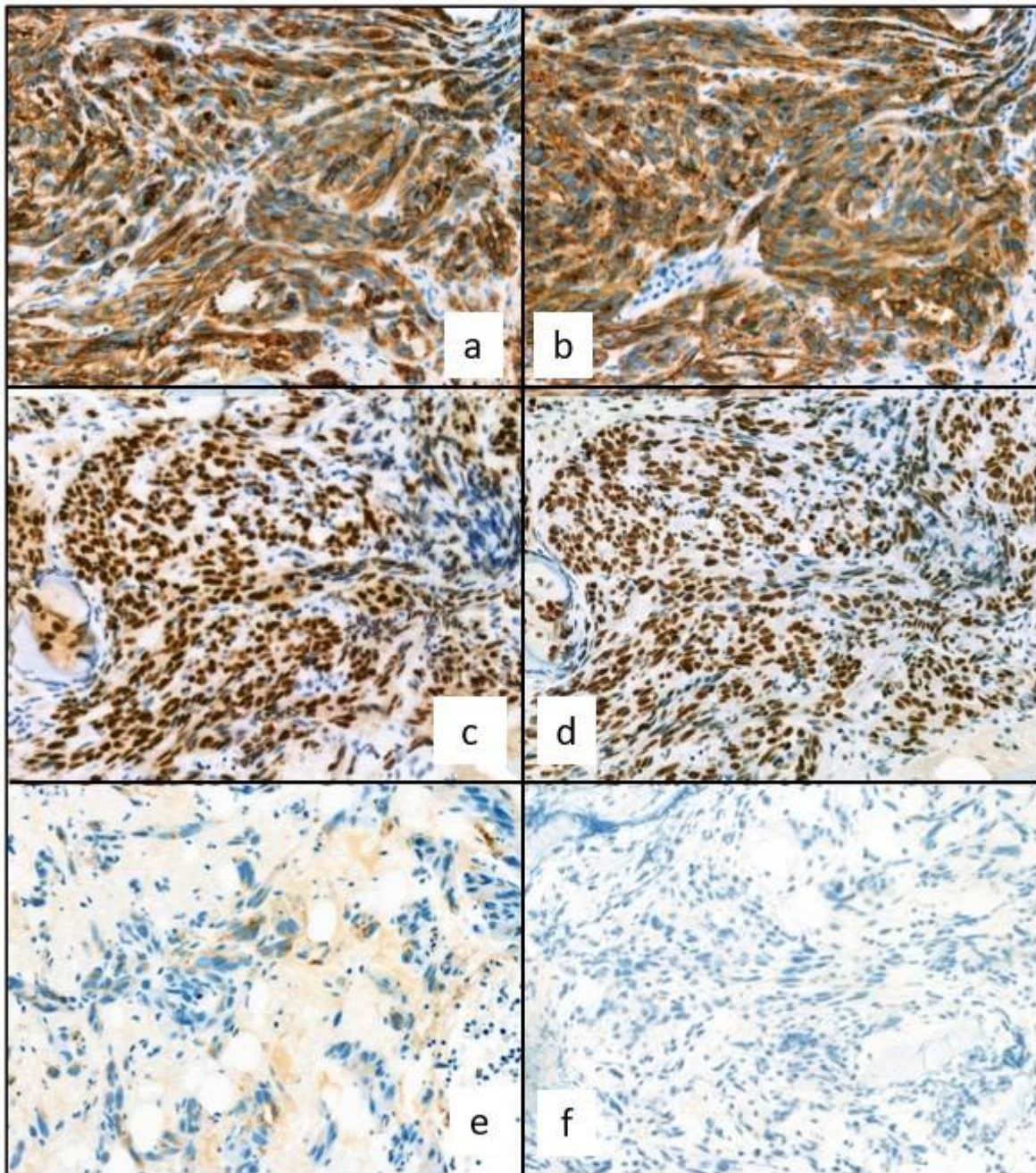


**Figure 1.** Portovenous phase CT scan of the abdomen in coronal view (a) and axial view (b) demonstrate hepatosplenomegaly with multiple hypoenhancing hepatic and splenic masses. Bone window CT scan of the chest in axial view (c) revealed an osteolytic lesion at manubrium.

The patient was admitted with a differential diagnosis between hematologic malignancy and metastatic tumor. During admission, anemia and liver function worsened. A flow cytometry of marrow aspiration showed no evidence of lymphoproliferative disorder, while a histologic examination revealed replacement of marrow content by the spindle-shaped cells with occasional eosinophilic inclusions forming of solid architecture with few vascular luminal formations, which raised suspicions of metastatic malignant vascular tumor. (Figure 2) The differential diagnosis included metastatic angiosarcoma and Kaposi sarcoma.



**Figure 2.** Histologic appearance on low magnification shows marrow space occupied by spindle-shaped cells. (a, b) Higher magnification shows neoplastic spindle cells with markedly enlarged and hyperchromatic nucleus with few vascular channel formations. (c, d)



**Figure 3.** Immunohistochemical staining shows tumor cells were positive for CD31 (a), CD34 (b), ERG (c), FLI1 (d), weak focal positive for factor VIII (e) but negative for HHV-8 (f).

Immunohistochemical stains (Figure 3) show that the tumor cells were positive for CD31, CD34, ERG and FLI1 with a weak focal positive for factor VIII and negative for HHV-8, desmin, smooth muscle actin, S100, CD117, CD61, CD71, myeloperoxidase, CD3, CD20 and CD30, thus excluding Kaposi sarcoma and lymphoma. The final diagnosis was given as metastatic angiosarcoma, in which the primary site could either be the liver or spleen. After progressive clinical deterioration, the patient passed away 11 days after admission and no autopsy was permitted.

## Discussion

Angiosarcoma is a malignant tumor with functional and morphological features of normal endothelium. It accounts for less than 1% of all sarcomas. The tumor is classified into multiple subtypes based on primary site with cutaneous angiosarcoma being the most common<sup>(1-3)</sup>. In the present case, no cutaneous angiosarcoma was detected. The patient had only two potential organs that could be the primary site of primary angiosarcoma; the liver or spleen.

Hepatic angiosarcoma is the most common sarcoma of the liver but accounts for only 2% of primary hepatic malignancy<sup>(4)</sup>. The disease usually occurs in older males in their sixth to seventh decade of life, with varied clinical presentations ranging from asymptomatic to liver failure. Approximately 25%-40% of reported cases of hepatic angiosarcoma are associated with exposure to thorotrast, arsenic, vinyl chloride or steroids. Splenic angiosarcoma is less common with an estimated incidence of 0.14 to 0.25 per million per year<sup>(4-6)</sup>. Both subtypes have poor prognosis with around 3% of hepatic angiosarcoma patients surviving longer than two years after diagnosis and almost all of splenic angiosarcoma patients die within 12 months<sup>(5,6)</sup>.

Most cases present with metastatic disease in the liver and spleen. Typical CT imaging of the hepatic and splenic angiosarcomas include hepatomegaly and splenomegaly with multifocal hepatic/splenic lesions. The lesions typically appear as hypoattenuating nodules/masses on a non-contrast enhanced phase CT scan with or without hyperattenuating foci, representing hemorrhage. In contrast enhanced phase CT scans, the lesions demonstrate heterogeneous enhancement with heterogeneous progressive enhancement in the delayed phase<sup>(7,8)</sup>. Due to the hypervascularity nature of tumors, prominent vessels within the tumors or vascular invasion may be observed<sup>(8)</sup>. In this patient, the CT scan showed hepatosplenomegaly with multiple hypoenhancing hepatic and splenic masses without an area of hyperenhancement or progressive enhancement in the delayed phase. These imaging findings are considered atypical for angiosarcoma, however, the patterns of enhancement can vary depending on pleomorphic histopathology of the angiosarcoma, which ranges from malignant endothelial cells forming vascular sinusoids to solid sheets of epithelioid cells without definite vasoformation<sup>(8,9)</sup>. In this situation, tissue diagnosis plays an important role. Furthermore, it is difficult to determine the primary site of disease when there is multifocal disease in the liver, spleen, and bone at initial presentation<sup>(8)</sup>. Moreover, metastatic angiosarcoma in the bone typically show osteolytic lesions with ill-defined margins, and involve the long bone<sup>(8)</sup>.

The appearance of angiosarcoma typically features heterogenous characteristics consisting of hemorrhagic, spongy, necrotic or solid-cystic cut surfaces. The hepatic subtype usually presents multiple nodules in both lobes while the splenic subtype can occupy the organ as a single nodule, multiple nodules or diffuse involvement.

Both hepatic and splenic angiosarcomas show infiltrative borders and the microscopic architecture could be vasoformative, solid or mixed. The vasoformative structure is filled with

blood with a sinusoidal, cavernous or papillary formation and is lined by malignant endothelial cells. The cells in both the endothelial and solid part are heterogeneous and pleomorphic with enlarged, hyperchromatic nuclei. Spindle or epithelioid cell features may be present. It was also noted that splenic angiosarcoma could have bland cytology. Frequent mitosis, necrosis and fibrosis are common and the malignant cell could invade normal adjacent blood spaces.

Confirmation with immunohistochemical staining is performed using a combination of CD31 and CD34. CD34 normally stains normal endothelium and vascular tumors but it can be expressed in the mesenchymal neoplasm such as the epithelioid sarcoma or dermatofibrosarcoma protuberans while CD31 positivity is more specific for angiosarcoma but it can be expressed in normal platelets, macrophages and plasma cells<sup>(1-3)</sup>. Newer stains include FLI1 and ERG. FLI1 is more sensitive but it can be expressed in some adenocarcinoma and melanoma<sup>(1-2,4)</sup>. ERG is sensitive for vascular differentiation<sup>(1-2,4)</sup>. Both markers are suggested as secondary stains to the CD31 and CD34. In our case, all these markers are positive and the lack of HHV8 (LANA) excludes Kaposi sarcoma.

Tumor metastasis in angiosarcoma is a common presentation due to aggressive behavior and delayed diagnosis. Common metastatic sites in hepatic angiosarcoma are the lungs, lymph node and spleen while those in splenic angiosarcoma are the lungs, liver and lymph nodes<sup>(4)</sup>. But metastatic angiosarcoma to bone marrow is rare with only a few case reports in English literature; and most of them are from primary splenic angiosarcoma<sup>(10-13)</sup>. Our report contributes an additional case report to the possible rare clinical manifestation in angiosarcoma. The case also emphasizes diagnostic problems between angiosarcoma and other malignancies with vascular differentiation.

## **Acknowledgement**

This case report would not have been possible unless we were supported by the Departments of Nuclear Medicine, of Radiology and of Pathology at Aster MIMS, Kozhikode, Kerala, India and Dr Ajith Bhaskar, a pulmonologist in Kozhikode, Kerala, India.

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## **Funding statement**

The authors declare no conflict of interest in preparing this article

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## **APPENDIX 1**

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The original articles are the researches describing the novel understanding of anatomical pathology, clinical pathology (laboratory medicine), forensic medicine (legal medicine or medical jurisprudence), molecular medicine or pathobiology. Systematic reviews, meta-analyses and clinical trials are classified as articles. The articles should be clearly and concisely written in the well-organised form (see ***Organisation of Manuscripts***): abstract; introduction; materials and methods; results; discussion; and conclusions. The manuscripts that have passed an initial screening by the Editorial Board will be reviewed by two or more experts in the field.

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The manuscripts written in English language are preferable. However, Thai papers are also acceptable, but their title pages, abstracts, and keywords must contain both Thai and English. These English and Thai manuscripts are prepared in A4-sized Microsoft Word documents with leaving 2.54-cm (1-inch) margins on all sides. All documents are required to be aligned left and double-spaced throughout the entire manuscript. The text should

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A structured form of abstract is used in all Original Article manuscripts and must include the following separate sections:

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- *Results: The main findings*
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The Introduction section should clearly explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

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The Materials and Methods section must be described in sufficient detail to allow the experiments or data collection to be reproduced by others. Common routine methods that have been published in detail elsewhere should not be described in detail. They need only be described in outline with an appropriate reference to a full description. Authors should provide the names of the manufacturers and their locations for any specifically named medical equipment and instruments, and all chemicals and drugs should be identified by their systematic and pharmaceutical names, and by their trivial and trade names if relevant, respectively. Calculations and the statistical methods employed must be described in this section.

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The Discussion section should focus on the interpretation and the significance of the findings against the background of existing knowledge. The discussion should not repeat information in the results. The authors will clearly identify any aspects that are novel. In addition, there is the relation between the results and other work in the area.

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The Conclusion section should state clearly the main summaries and provide an explanation of the importance and relevance of the study reported. The author will also describe some indication of the direction future research should take.

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The Acknowledgements section should be any brief notes of thanks to the following:

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- *A person who provided purely technical help or writing assistance*
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- *Books*

2. Remington JS, Swartz MN. *Current Topics in Infectious Diseases*, Vol 21. Boston: Blackwell Science Publication, 2001.

- *Chapter in a book*

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## 11. Tables

The tables should be self-contained and complement, but without duplication, information contained in the text. They should be numbered consecutively in Arabic numerals (Table 1, Table 2, etc.). Each table should be presented on a separate page with a comprehensive but concise legend above the table. The tables should be double-spaced and vertical lines should not be used to separate the columns. The column headings should be brief, with units of measurement in parentheses. All abbreviations should be defined in footnotes. The tables and their legends and footnotes should be understandable without reference to the text. The authors should ensure that the data in the tables are consistent with those cited in the relevant places in the text, totals add up correctly, and percentages have been calculated correctly.

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- *Figure Legend (s)*
- *Figure (s)*

#### 14.6. Technical Notes

The Technical Note manuscripts consist of the following order:

- *Title Page*
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- *Main text*
- *Conclusions*
- *Acknowledgements*
- *References*
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