



UNDIAGNOSED FATAL MALIGNANCIES IN ADULT AUTOPSIES: A 5-YEAR RETROSPECTIVE HISTOPATHOLOGICAL STUDY

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ABSTRACT **Introduction:** Autopsies reveal undiagnosed malignancies even in this era of modern diagnostic imaging and ancillary laboratory studies. This study has been carried out to study the incidence of clinically undiagnosed malignancy on autopsy and even search for primary lesions in case of incidental secondary lesions on autopsy. **Materials and Methods:** Present was a retrospective, non-interventional and cross section study conducted at Department of Histopathology, Government Medical College, Akola over a period of five years from July 2015 to June 2020. All pathological areas were adequately sampled and sections stained with Hematoxylin and Eosin (H&E) were studied. Wherever needed special stains were also performed. **Results:** Out of total 1176 autopsies performed and studied over five-years study period, 15 cases (1.27%) were found to be of clinically undiagnosed malignancies. We found ten males and five females in these 15 cases. Out of 15 cases, 13 were in the age group of 55-75 years. **Conclusion:** Efforts are being made to restore the autopsy to an appropriate level of utilization for the benefit of humankind.

KEYWORDS : Autopsy, Adult, Clinically undiagnosed, Malignancy, Histopathology

INTRODUCTION:

An autopsy is the examination of the body of a dead person. Autopsies are performed to determine the cause of death, for legal purposes, education and research. The clinical autopsy rate has dropped from 50% to less than 10% over the past 50 years.¹ Multiple factors such as lack of reimbursement, cultural and religious objections by families, and increasing workload for house staff, account for the decrease.² Even as sophisticated medical technologic tools have been developed and made available, the role of the autopsy for confirming clinical diagnoses and identifying unsuspected findings should be reevaluated regularly.³ Autopsies are performed by Pathologists, Medical Doctors who have received specialty training in the diagnosis of diseases by the examination of body fluids and tissues. An autopsy may be restricted to a specific organ or region of the body.¹

"Virtopsy" is a word combining 'virtual' and 'autopsy', it employs imaging methods that are also used in clinical medicine such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) for the purpose of autopsy, to find the cause of death. Virtopsy can be employed as an alternative to standard autopsies for broad and systemic examination of the whole body as it is less time consuming, aids better diagnosis and renders respect to religious sentiments.⁴

Carcinoma of unknown primary origin (CUP) is a heterogeneous group of cancers defined by the presence of metastatic disease with no identified primary tumor at presentation.⁵ Some malignancies are not detected clinically due to lack of any symptoms and may be the primary cause of death. Autopsies reveal undiagnosed malignancies even in this era of modern diagnostic imaging and ancillary laboratory studies.⁶ It becomes an easy task to search for primary lesion with possible metastasis when the given cause of death is malignancy. But for the unknown cause of death it is the expertise, experience and alert attitude of Histopathologist to note every single, minute finding on thorough external examination of cadaveric body and its internal organs, which may awake alert sign to consider malignancy to be one of the cause of death.

The incidence of clinically undiagnosed malignancies related to primary cause of death has rarely been studied. Considering these findings and observations, this study has been carried out to study the

incidence of clinically undiagnosed malignancy on autopsy and even search for primary lesions in case of incidental secondary lesions on autopsy.

MATERIAL AND METHODS:

Present was a retrospective, non-interventional and cross section study conducted at Department of Histopathology, at a Tertiary Care Center over a period of five years from July 2015 to June 2020. Retrospective data of 1176 cases (Medico-legal and Clinical) was collected from postmortem reports. All autopsy cases irrespective of the cause of death were included. However, partial and completely autolyzed specimens were excluded. Total of 15 cases of Caucasian race were included in the study, out of which ten were male and five were female, with the minimum age of 20-years and maximum of 75-years. Detailed Medical and Clinical history was obtained from records. Dietary habits and lifestyle of the cases were also correlated, wherever possible, to the type of malignancy diagnosed in the case. All the organs received, were weighed, dimensions were noted and fixed in 10% formalin. In gross examination, organs were meticulously observed for color, consistency, scarring, fibrosis, nodules, infarcts, secretions, edema, granulomas, adhesions and abscess cavities. All pathological areas were adequately sampled. Paraffin blocks were made. 4-5 micron thin sections stained with Hematoxylin and Eosin (H&E) were studied. Wherever needed, special stains like PAS, Ziehl Neelsen (ZN), Congo Red, Masson's Trichrome, Mucicarmine and Reticulin were also performed and studied.⁷

There was no statistical analysis done in the present study, as the number of cases were insufficient to run the statistics.

OBSERVATIONS AND RESULTS:

Out of total 1176 autopsies performed and studied over five-years study period, 15 cases (1.27%) were found to be of clinically undiagnosed malignancies.

Table 1: Distribution of cases according to age and sex with their metastatic site (n=15)

Diagnosis	Age (years)	Male	Female	Metastatic site	Total
Acute Lymphoid Leukemia	20	-	1	Fallopian tubes and ovaries	1

Left Atrial Myxoma	30	1	-	-	1
Hepatocellular carcinoma liver	56	1	-	-	1
Adenocarcinoma lung	59	-	1	-	2
	70	1	-	Liver	
Squamous cell Carcinoma of oesophagus	65	1	-	-	2
	70	1	-	Lung	
Bilateral serous cystadenocarcinoma ovary	65	-	1	Liver, Lungs and Spleen	1
Adenocarcinoma colon	65	-	1	Bilateral ovaries (Krukenberg's) with ascites	1
Chromophobe Renal cell carcinoma	68	1	-	-	1
Squamous cell carcinoma lung	68	1	-	-	3
	70	1	-	-	
	72	1	-	-	
Collecting duct carcinoma kidney	70	-	1	-	1
Malignant mesothelioma heart	75	1	-	-	1
Total		10	05		15

Table 1 shows, we found ten male and five female cases. Thus, male to female ratio was 2:1. Out of 15 cases, 13 were in the age group of 55-75 years.

There was one interesting case of Acute Lymphoid Leukemia (ALL) diagnosed incidentally in a 20-year maternal death with ruptured ectopic pregnancy in fallopian tube, showing leukemia infiltrate in both fallopian tubes (Fig 2K) and ovaries. She belonged to low socio-economic strata and also presented with anemia. Another case was an incidentally found 2×1 cm soft gelatinous mass in left atrium which turned out to be myxoma on microscopy. He was 30-year-old who presented with sudden cardiac death. This was the only benign neoplasm detected in this study duration. Although a benign tumor, reports on its malignancy are well-known, which include: (i) local relapse (ii) local invasiveness and (iii) distant metastasis.⁸

One rare autopsy finding was seen in a 75-year male beggar who presented with sudden cardiac death, showing malignant mesothelioma of heart on microscopy (Fig 2G) and multiple nodular thickening of pericardium on gross examination.

Hepatocellular carcinoma (HCC) liver was found in 56-year male who was a known case of cirrhosis liver on treatment with a single liver nodule on autopsy, that turned out to be malignant on microscopy. He was a chronic alcoholic with a history of daily intake of alcohol, since 40-years.

Multiple metastatic lesions (Fig 1E, 1F) were discovered in liver in a 70-year male. On through examination and study of multiple sections from all organs, primary lesion of adenocarcinoma was found to be present in lungs. This case proves the importance of practice of studying multiple sections of organs at autopsy.

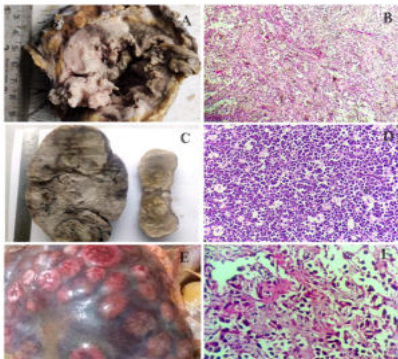


Figure 1: Gross and microscopic pictures of autopsy malignancies

- A – Gross lesion of Collecting Duct Carcinoma of Kidney
- B – Microphotograph of Collecting Duct Carcinoma of Kidney (H&E, 200x)
- C – Gross appearance of bilateral Serous Cystadenocarcinoma of Ovary
- D – Microphotograph of Serous Cystadenocarcinoma of Ovary (H&E, 200x)
- E – Multiple metastatic lesions in Liver
- F – Microphotograph of metastatic Adenocarcinoma in Liver (H&E, 400x)

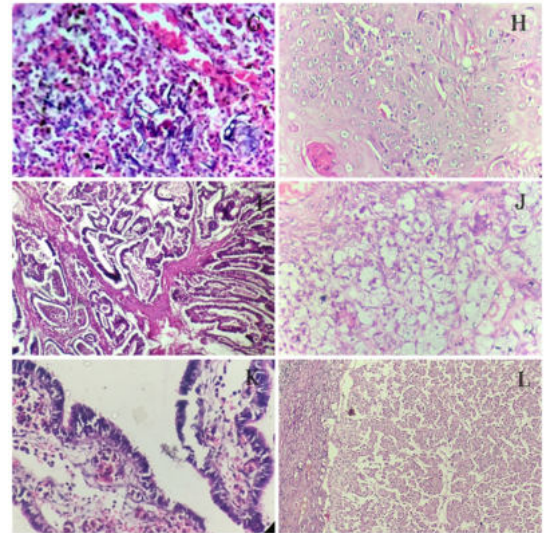


Figure 2: Microscopic pictures of autopsy malignancies

- G – Microphotograph of Malignant Mesothelioma of Heart (H&E, 200x)
- H – Microphotograph of Squamous Cell Carcinoma of Oesophagus (H&E, 400x)
- I – Microphotograph of Adenocarcinoma of Colon (H&E, 200x)
- J – Microphotograph of Krukenberg's tumour of Ovary (H&E, 200x)
- K – Microphotograph of Acute Lymphoid Leukemia in Fallopian tube (H&E, 200x)
- L – Microphotograph of Chromophobe Renal Cell Carcinoma (H&E, 200x)

Out of three cases of squamous cell carcinoma (SCC) lung, one case was 70-year male, who was a known case of Pulmonary Koch's on treatment.

All these four cases of lung malignancy, were found to be chronic smokers.

We reported two cases of carcinoma esophagus (Fig 2H). One was 65-year male, who belonged to poor family and was on treatment for acute hepatitis and died during treatment and other was 70-year skinny male with secondaries in lungs. He had a low dietary intake of fruits. Both were clinically undiagnosed cases of malignancy.

One clinically undiagnosed case of bilateral serous cystadenocarcinoma ovary (Fig 1C, 1D) with multiple metastatic lesions in liver, lungs and spleen was reported. Also, there was a 65-year female with a primary adenocarcinoma of colon (Fig 2I), having secondaries in bilateral ovaries (Krukenberg's) (Fig 2J) and malignant ascites. She had high dietary intake of meat (non-vegetarian).

In kidney, we found one case each of Chromophobe Renal Cell Carcinoma (RCC), with a history of tobacco chewing and cigarette smoking (Fig 2L) and collecting duct carcinoma (Fig 1A, 1B), both being clinically undiagnosed.

DISCUSSION:

In the present study, we found 1.27% of clinically undiagnosed malignancies. While it was different in different studies in literature, like 18.2% in study done by Hyejong Song Marshall⁷ from USA, 11% in study done by B. Karwinski et al⁹ in Norway and 3.1% in study by Shobha Parajuli et al⁶ from USA (Table 2).

Table 2: Comparison Of Incidence Of Undiagnosed Malignancies On Autopsy In Different Countries

Study	Country	Undiagnosed malignancy (%)
Hyeong Song Marshall ¹	USA	18.2
B. Karwinski et al ⁹	Norway	11
Shobha Parajuli et al ⁶	USA	3.1
Present study	India	1.27

Leukemic involvement of ovary has been found in up to 30% of patients with acute lymphocytic leukemia (ALL) at autopsy, but is rarely found clinically. Since the ovary may be a sanctuary for ALL to reseed the marrow, early clinical detection of ovarian involvement is important.¹⁰ There was a 20-year maternal death in present study who presented with fallopian tube ectopic pregnancy, which revealed leukemic infiltrates in both the tubes and ovaries. She was an undiagnosed case of ALL and microscopy revealed co-existence of ALL with ectopic pregnancy.

Primary cardiac tumors are rare, accounting for 0.0017-0.03% in autopsy series, in contrast to metastatic tumors of the heart, which are 30 times more frequent. Clinical manifestations of cardiac myxoma (CM) are protean and may vary from asymptomatic cases to unexpected sudden death (generally caused by blood flow obstruction or embolization). CM occur more frequently among women in the fifth or sixth decade of life and develop in left atrium in 75% of cases.¹¹ Present study showed one 30-year male with left atrial myxoma, who presented with sudden cardiac death. Kalgi Modi et al¹² had also reported one case of left atrial myxoma with sudden death. Primary pericardial mesothelioma (PPM) is exceptionally rare with an incidence of only 0.0022% in a series of nearly 500,000 random autopsies. The diagnosis of PPM is usually difficult and late, and in majority it is typically made at autopsy.¹³ Malignant pericardial mesotheliomas account for up to 50% of primary pericardial tumors.¹⁴ Similar to the case reports in literature,^{13,14,15} present study also found a case of 75-year male of malignant mesothelioma of heart with sudden cardiac death, diagnosed incidentally at autopsy.

HCC accounts approximately 5.4% of all cancers, with highest incidence in Asian countries. Peak incidence is seen in between 20 and 40 years of age and in almost 50% of cases, tumor appears in the absence of cirrhosis. Liver cell carcinoma is fifth leading cause of death in males. Chronic liver diseases are most common setting for emergence of HCC.¹⁶ We too had a case of 56-year male of HCC with cirrhosis, incidental diagnosis at autopsy. Bal MS¹⁷ reported three cases of metastatic adenocarcinoma in liver.

Carcinoma lung peaks in 50s and 60s of age and about 80% are seen in active smokers. Adenocarcinoma of lung is now more common, seen in females.¹⁶ In present study, we reported one case each in elderly male and female for adenocarcinoma lung is 59-year female and there were three cases of SCC lung, all in male (Table 1). Tahir et al¹⁸ reported two cases of SCC lung and one case of metastatic adenocarcinoma in lung in an elderly female case.

SCC of esophagus is most common worldwide, in males above 45 years of age. Adenocarcinoma of esophagus is limited to mucosa and submucosa.¹⁶ Both the cases of esophageal malignancy in present study were elderly males, one with metastatic lesions in lungs.

Colorectal adenocarcinoma is responsible for nearly 10% of all cancer deaths.¹⁶ Present study found a 65-year female with adenocarcinoma colon having Krukenberg's tumor and malignant ascites. Also, there was a case with bilateral serous cystadenocarcinoma of ovary along with multiple secondary lesions in lungs, liver and spleen. Serous cystic neoplasms include the most common malignant ovarian tumors. Serous carcinomas occur later in life on average, but often occur at earlier ages in familial cases. High-grade tumors are often widely metastatic throughout the abdomen at the time of presentation.¹⁶

RCC occurs in sixth and seventh decades of life with 2:1 male preponderance. While collecting duct carcinoma accounts approximately 1% or less of the renal epithelial neoplasms but have very aggressive behaviour.¹⁶ We had both the cases with renal neoplasms in their sixth decade of life. Sandhu et al¹⁹ found two cases of RCC on autopsy.

CONCLUSION:

For years together autopsy studies have immensely added to the

knowledge of Pathologists and Clinicians. Autopsy study made upon undiagnosed neoplasms though rare is very useful to give a definite cause of death as prevalence of cancer is increasing worldwide at all ages and both sex. Histopathology remains the Gold Standard to diagnose all clinically occult malignancies with the practice of studying multiple sections from all organs, as no organ in the human body is spared from being a sanctuary of either primary or metastatic malignancy.

With the renewed and increased recognition of the continuing value of a thoughtfully performed and reported autopsy, efforts are being made to restore the autopsy to an appropriate level of utilization for the benefit of humankind.

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