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Association of clinicopathologic features with metastasis in clear cell renal cell carcinoma

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Abstract

Objective: Metastasis is the most important prognostic indicator for clear cell renal cell carcinoma patients. The higher incidence of metastasis the higher incidence of death rate. To decrease death rate, understanding clinicopathologic features associated with clear cell renal cell carcinoma metastasis is required.

Materials and Methods: Cross-sectional study was conducted to 40 cases of clear cell renal cell carcinoma in the Anatomical Pathology Department of Faculty of Medicine, Universitas Padjadjaran/ Hasan Sadikin Hospital. To examine association between metastasis and clinicopathological features data were analyzed used Chi-Square test. P value ≤0.05 was considered significant.

Results: Coagulative necrosis have associations with metastasis in clear cell renal cell carcinoma with significant result (p=008)

Conclusions: Coagulative necrosis was associated with metastasis in clear cell renal cell carcinoma and may show the sign of tumor cell aggressiveness during metastasis process.

Keywords: clear cell renal cell carcinoma, metastasis, coagulative necrosis

Introduction

Clear cell renal cell carcinoma (ccRCC) is the most common RCC subtype, originating from kidney epithelial tubules [1]. However it is the most lethal urologic malignancy with an annual mortality rate of 50% an annual incidence of 403.262 new cases worldwide [2]. This is a highly heterogeneous tumor with different clinical behaviour and characteristics that remain unpredictable [3]. Many prognostic factors for ccRCC are known and numerous prognostic models have been developed in an attempt to predict which patients ultimately will develop advanced disease. Metastasis is the most important prognostic indicator and responsible for 90% mortality [4, 5]. In this study, ccRCC cases diagnosed in 6 years were investigated cross sectionally. The objective of this study was to describe the epidemiological and clinicopathologic characteristics of ccRCC to identify the clinicopathologic variables associated with the occurrence of metastasis.

Subjects and Methods

The research material is formalin-fixed paraffin-embedded tissue (FFPE) of patients who have undergone radical nephrectomy and has been diagnosed histopathologically as ccRCC period between January 1st, 2014 until November 31st, 2020 at DR. Hasan Sadikin General Hospital, West Java, Indonesia. Ethical clearance was approved from Health Research Ethics Committee of Faculty of Medicine Universitas Padjadjaran with waiver of informed consent (LB.02.01/X.6.5/357/2020). All clinicopathologic data were retrieved from medical records at Department of Urology and from pathology records from the Institute of Pathology at the same institution. Clear cell renal cell carcinoma was defined according to American Joint Committee on Cancer as a morphologically heterogeneous group of malignant neoplasms, with solid alveolar and acinar patterns being most common, composed of cells with clear or eosinophilic cytoplasm which is commonly filled with lipids and glycogen and contain a regular network of small, thin-walled blood vessels, a diagnostically helpful characteristic of this tumour [6]. Clinicopathological parameters included in the analysis were: age, sex, grading, coagulative tumor necrosis, and rhabdoid or sarcomatoid differentiation. Age was defined as age at the first time diagnosis. Sex was defined as male or female. Grading system used in this study was based on WHO/ International Society of Urological Pathology (ISUP) grading system for ccRCC. Coagulative tumor necrosis was defined as the presence of microscopic coagulative necrosis. The presence of necrosis apparent on gross examination was not included in our assessment because the appearance of a central, fluid filled space within a tumor may result not only from necrosis, but also from hemorrhage or cystic degeneration. In addition, the presence of histopathologic regressive changes, such as cystic transformation, hyalinization, and fibrosis, were not considered as necrosis [7]. Sarcomatoid differentiation within ccRCC was defined as a spindle cell malignancy that had the histologic appearance of a sarcoma. Rhabdoid differentiation was defined round, oval cell malignancy that had the histologic appearance of a rhabdomyosarcoma [6]. Metastasis was defined as tumor finding in other sites based on radiologic imaging, cytologic features from pleural effusions or fine needle aspirations biopsy on tumor secondary sites from the first time diagnosis until this study was started. The routine pathologic assessment of ccRCC specimens was based on a minimum of 3 formaline-fixed, paraffin-embedded tissue blocks per tumor. Necrosis was quantitatively assessed by “eye-ball” estimation, and only nephrectomy specimens with >90% necrosis were

included for the purposes of this study. The microscopic slides from all specimens were reviewed by an urologic pathologist (S.S) with a CX21 microscope (Olympus, Optical Corporation, Melville, NY) without knowledge of patient outcome, after 2 collaborative sessions at a multiheaded microscope to standardize interpretations of coagulative tumor necrosis.

Statistical Analyses

The relationship between coagulative tumor necrosis and other clinicopathologic parameters was studied by nonparametric tests. All statistical analyses were performed using the Statistical Package for Social Sciences, version 17.0 (SPSS, Chicago, IL). P value less than 0.05 was considered statistically significant.

Results

Patient's Characteristics

In this study, total samples number were 95 consists of 63 cases of radical nephrectomy and 32 cases of biopsy. We only take nephrectomy cases in order to analyse the extent of tumor necrosis but only 40 were eligible. Inclusion criteria were FFPE available in the department, sufficient tissue in the FFPE, and complete clinical information in medical record.

Table 1: Research Subject Characteristic

Variable	N=40
Age (years) Mean±SD	51±13.41
Sex	
Male	29 (72.5%)
Female	11 (27.5%)
Metastasis	
Yes	20 (50%)
No	20 (50%)
Grading ISUP	
1	0 (0%)
2	16 (40%)
3	16 (40%)
4	8 (20%)
Coagulative Tumor Necrosis	
Yes	14 (35%)
No	26 (65%)
Rhabdoid Differentiation	
Yes	6 (15%)
No	34 (85%)
Sarcomatoid Differentiation	
Yes	2 (5%)
No	38 (95%)

Association of Metastasis on Clear Cell Renal Cell Carcinoma with Patients Characteristic.

The association between metastasis on ccRCC and patient's characteristic was analyzed. Coagulative tumor necrosis have associations with metastasis on ccRCC with significant result (p=0.008). No significant association was seen between metastasis and other characteristic patient, such as patient age, sex, grading ISUP, sarcomatoid differentiation, and rhabdoid differentiation. (p>0.05, table 2)

Table 2: Association of Clinicopathological Characteristics and Metastasis on Clear Cell Renal Cell Carcinoma

Variable	Metastasis	Non metastasis	P Value
Age (years) Mean±SD	51.45±13.14	51.05±14.01	P=0.818
Sex			
Male	15 (75%)	14 (70%)	P= 0.723
Female	5 (25%)	6 (30%)	
Grading ISUP			
1	0 (0%)	0 (0%)	P= 0.631
2	10 (50%)	6 (30%)	
3	7 (35%)	9 (45%)	
4	3 (15%)	5 (25%)	
Coagulative Tumor Necrosis			
Yes	12 (60%)	2 (10%)	P = 0.008*
No	8 (40%)	18 (90%)	
Rhabdoid Differentiation			
Yes	1 (5%)	5 (25%)	P=0.077
No	19 (95%)	15 (75%)	
Sarcomatoid Differentiation			
Yes	3 (15%)	0 (0%)	P=0.072
No	17 (85%)	20 (100%)	

**Chi Square Test in SPSS for windows.* P value <0.005 is considered significant.

Discussion

Regardless of the recently develop in worldwide medical management, malignant tumor remain a crucial threat to human health. Clear cell renal cell carcinoma is the most lethal urological cancer with unpredictable behavior. Greater than one third of all patients who undergo definitive treatment for localized tumor will eventually confront a relapse of their disease secondary to metastatic disease progression. Therefore, precise prognostic prediction is paramount for identifying patients at greatest risk of progression and death in order to choose an appropriate management of ccRCC patients [5]. Currently, the diagnostic and prognostic assessment of ccRCC based on pathologic examination and TNM classification system, regardless of the advances in identification of genetic and cellular changes in ccRCC. The identification of molecular changes can be a guidance in diagnostic and therapeutic decisions, but the limitation is high cost and time consuming. Consequently, none of the markers are routinely used in daily practice. Histopathological parameters, for example like tumor grading, coagulative tumor necrosis, rhabdoid or sarcomatoid differentiation are the easiest and simplest way to assess without any additional cost, thus it remains to be choosen in daily application [7]. Coagulative tumor necrosis are a local histopathological reflection of the cancer cell aggressiveness. Currently, Khor et el. reported that coagulative tumor necrosis have gained increasing attention in the prognostic prediction of ccRCC by adding to grade [8-10]. Coagulative tumor necrosis also considered as a prognostic parameter in other solid tumor such as carcinoma of the breast, transitional carcinomas of the upper urinary tract, colorectal, and lung cancer [7]. Coagulative tumor necrosis characterized by coalescent of homogeneous clusters and sheets of dead and degraded tumor cells into a solid, not

Apparently crystalline coagulum with associated viable tumor, typically high grade, adjacent to areas of necrosis. Frequently, remaining cell outline were noticed and the structure of nuclei were contracted and fragmented with increased in cytoplasmic granularity and eosinophilia. Dead and degraded tumor cells were blended into a lump of material formed from the content of a liquid, admixed with debris of nuclear and cytoplasmic [8]. There are several pitfall in determining coagulative tumor necrosis in ccRCC such as hemorrhage and dense eosinophilic fbrous tissue or hyalinized connective tissue. Hemorrhage marked by extravasated erythrocytes to the tumor interstitium. All this degenerative features have not to be mistaken for coagulative tumor necrosis. (Pictured) sBased on Table 2, coagulative tumor necrosis associates with ccRCC metastasis cases compared with non-metastasis cases. This finding was consistent with a hypothesis proposed in the 1970s, that coagulative tumor necrosis was acknowledged as a predictor of aggressive biologic behavior of RCC. This is also supported by Sengupta *et al*. that concluded from 3009 RCC patients that a coagulative tumor necrosis portends a poor prognosis [8]. Moch *et al*. reported poor patient outcome in 37% of 487 ccRCC patients with coagulative tumor necrosis. Other studies reported that the presence of coagulative tumor necrosis are 2 to 3 times more likely to die from RCC [8]. Pichler *et al* reported from 2.333 sample RCC patients that the presence of tumor necrosis is an independent predictor of clinical outcome in clear cell and papillary Not other type [7]. Majority of the previous study revealed that coagulative tumor necrosis associated with poor prognosis, but discordant finding in the literature because there is no considering about the subtype, grading, and cases with subtotal necrosis include different in quantifying the necrosis [11]. For example, Minervini *et al* divided tumor necrosis into 3 groups (1-30%, 30-75%, >75%) with statistically no significant association with prognosis.[12] Different with, Katz *et al*l divided tumor necrosis into 2 groups (<50%, >50%), with the Later group showing 2-fold increase in mortality related to cancer on multivariate analysis [13]. Coagulative tumor necrosis appear to indicate that tumor cell were growing rapidly that has overtaken its own vascular supplies [8]. Therefore, coagulative tumor necrosis is the consequence of inadequate vascularization and supply oxygenation into the tumor. On the other hand, coagulative tumor necrosis conceivably as the results of a host reaction which occurs for the purpose of defending against tumor. Tumors that forms, grows, or spread quickly can easily reveal necrosis, furthermore elevated the amount of lymphocyte that has moved from the blood into the tumor. The present of coagulative tumor necrosis can stimulate more vascularization within the tumor. Moreover, the leaky vasculature may facilitate the escape of tumor cells into the bloodstream promoting the establishment of metastases [14]. Coagulative tumor necrosis have gained increasing attention of many solid tumors such as lung, brain, and colon because tumor necrotic tissues. Might be directed target to ease both the hottest areas in external bioimaging and to enhance the treatment response of host immunity against tumor [15]. Hence, tumor necrosis useful as applicable biomarker for ccRCC antitumoral therapy. Nevertheless, this study has several strengths. First to maintain homogeneity we choose one histopathological subtype (ccRCC) and we only take samples from radical nephrectomy patients. Second, we choose all samples with strict inclusion and exclusion criteria.

Conclusion

This study underline the significance of coagulative tumor necrosis as a predictor of ccRCC metastasis. Therefore, coagulative tumor necrosis need to be consistently stated in pathological report and comprised as a predictive variable of metastasis for ccRCC.

Study limitations

The limitation of this study are the design and retrospective data collection which only 3 blocks per tumor. Recently, the most ideal guidance for gross sampling techniques is 1cm per section of the tumors. [3, 7] Coagulative tumor necrosis was not quantitatively measured, only absent or present. However, concerning above-mentioned limitations, our results show that coagulative tumor necrosis is a significant parameter with excellent accessibility and low costs, to predict metastases in ccRCC. This feature can be assessed as a selection criterion for risk stratification and decision-making to choose appropriate patient management of individualized treatment.

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Conflict of interest

The author declare that there is no conflict of interest regarding the publication of this paper.

Figure 1.a ISUP grade 1. Tumor nucleoli are absent or inconspicuous and basophilic at 400x magnification

Figure 1.b ISUP grade 2. Tumor nucleoli are conspicuous and eosinophilic at 400x magnification (right picture in circle) but not prominent at 100x magnification (left picture in circle)

Figure 1.c ISUP grade 3. Tumor nucleoli are eosinophilic and clearly visible at 100x magnification (in circle)

Figure 1.d ISUP grade 4. Tumor showing nuclear pleomorphism (left arrow) and rhabdoid differentiation characterized by large pleomorphic cells with abundant intensely eosinophilic cytoplasm and eccentrically placed hyperchromatic nuclei (upper cell) and large vesicular, centrally placed nuclei and prominent nucleoli (lower cell, insert picture) and coagulative tumor necrosis (right star)

Figure 2. Sarcomatoid differentiation. Spindle tumor cell, hypercellularity, and pleomorphic nuclei (arrow)

Figure 3.a Coagulative tumor necrosis identified by homogeneous clusters and sheets of degenerating and dead cells (upper right star), surrounded by viable tumor (left arrow)

Figure 3.b Coagulative tumor necrosis with shrunken or fragmented nuclei and increased cytoplasmic granularity and eosinophilia and increased cytoplasmic granularity and

eosinophilia (arrow)
Figure 3.c Coagulative tumor necrosis with coalescence of the cel into a coagulum admixed with nuclear and cytoplasmic debris (star) Figure 3.d Coagulative tumor necrosis with cholesterol cleft (star) Figure 4.b Degenerative change mimicking tumor necrosis, dense eosinophilic fibrous tissue (star) Figure 5 Mimicking feature of tumor necrosis, haemorrhage characterized by extravasated erythrocyte (star)

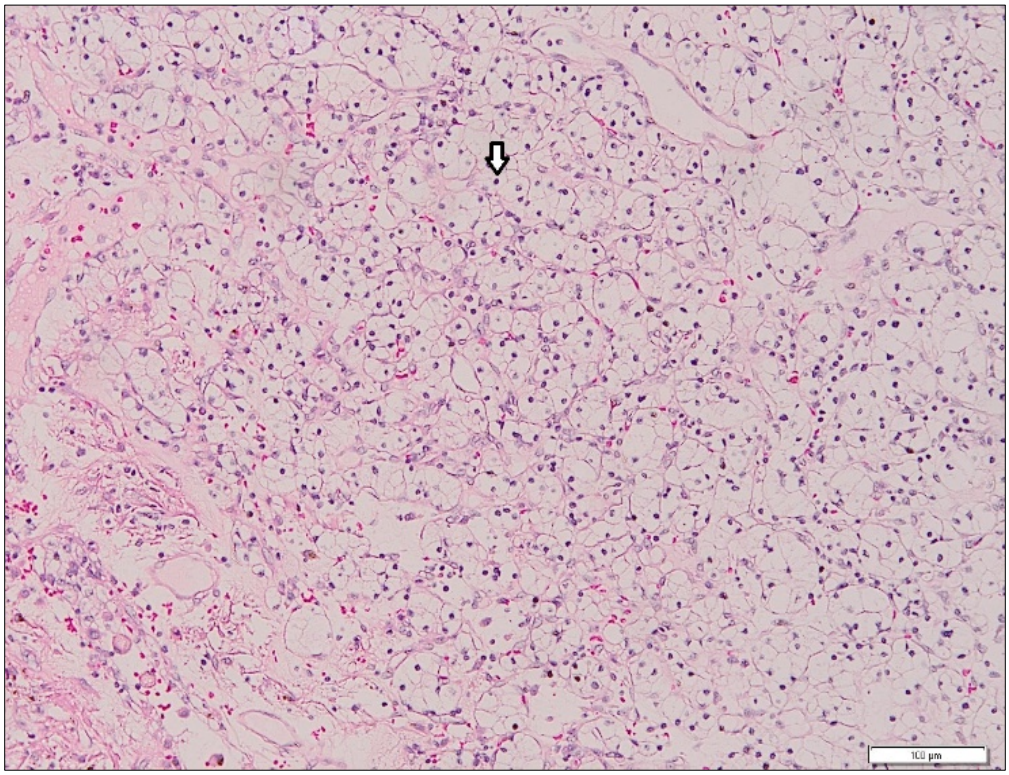

Fig 1

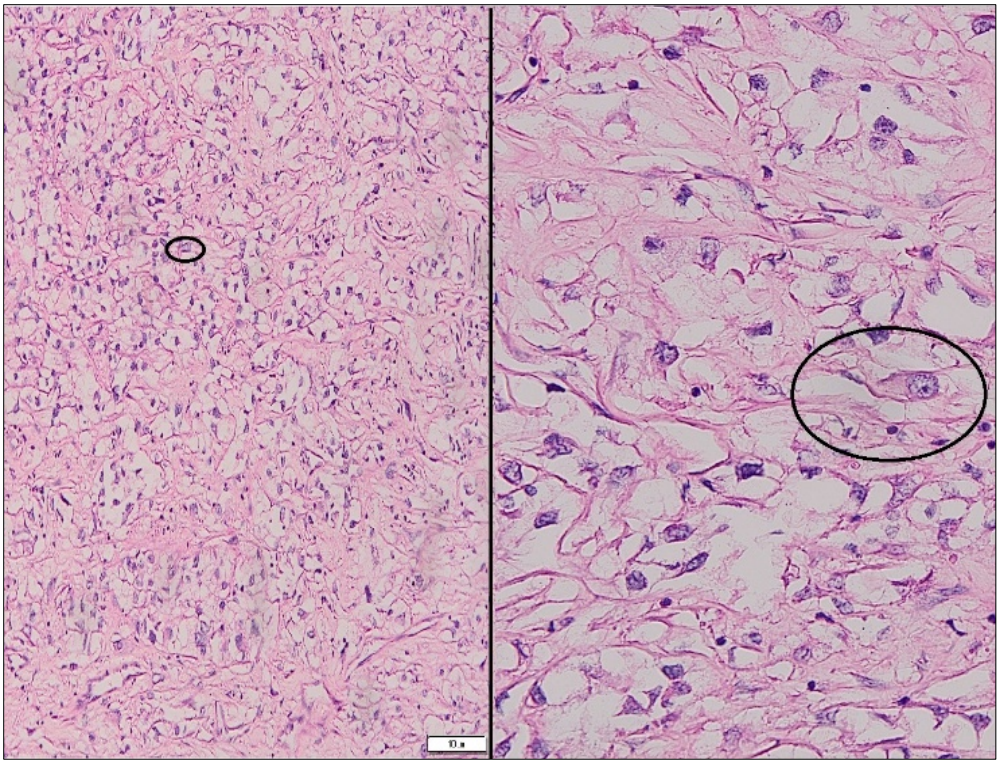

Fig 2

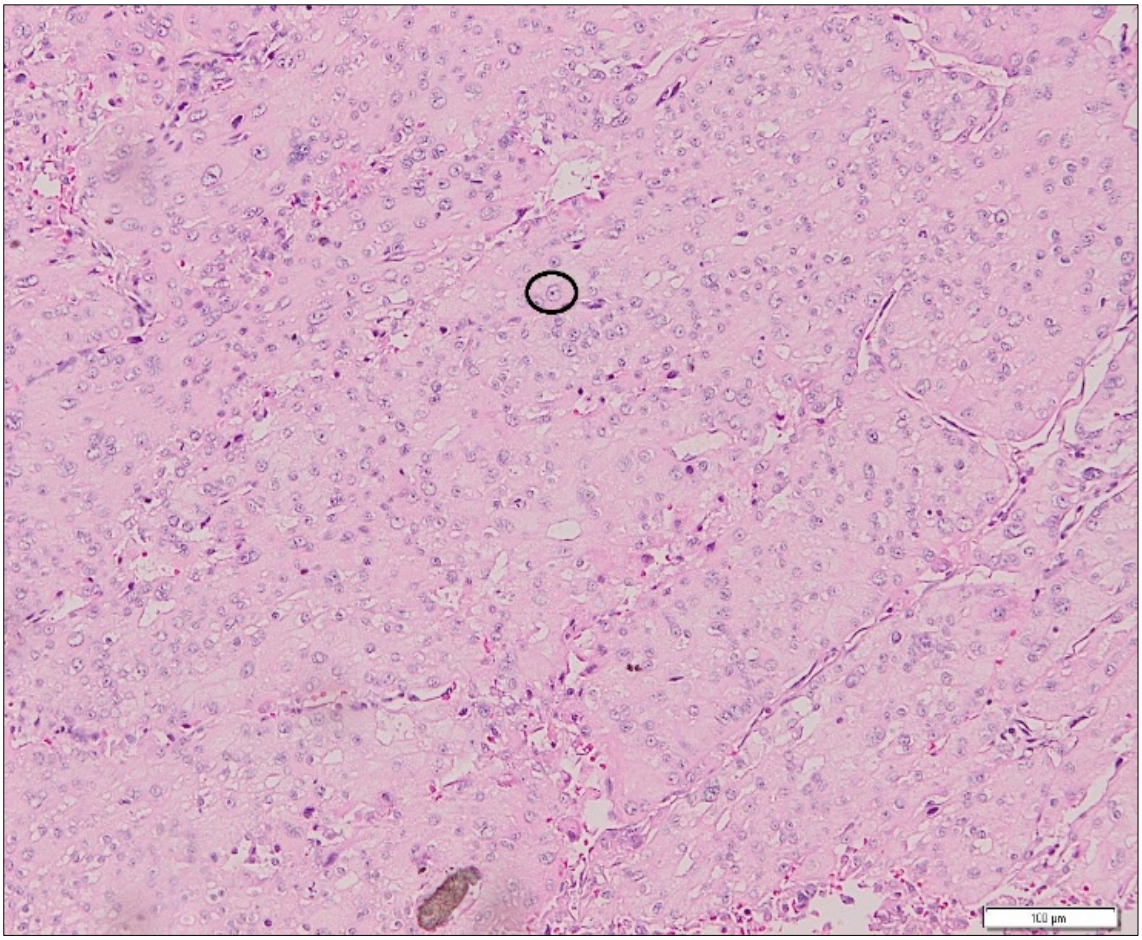

Fig 3

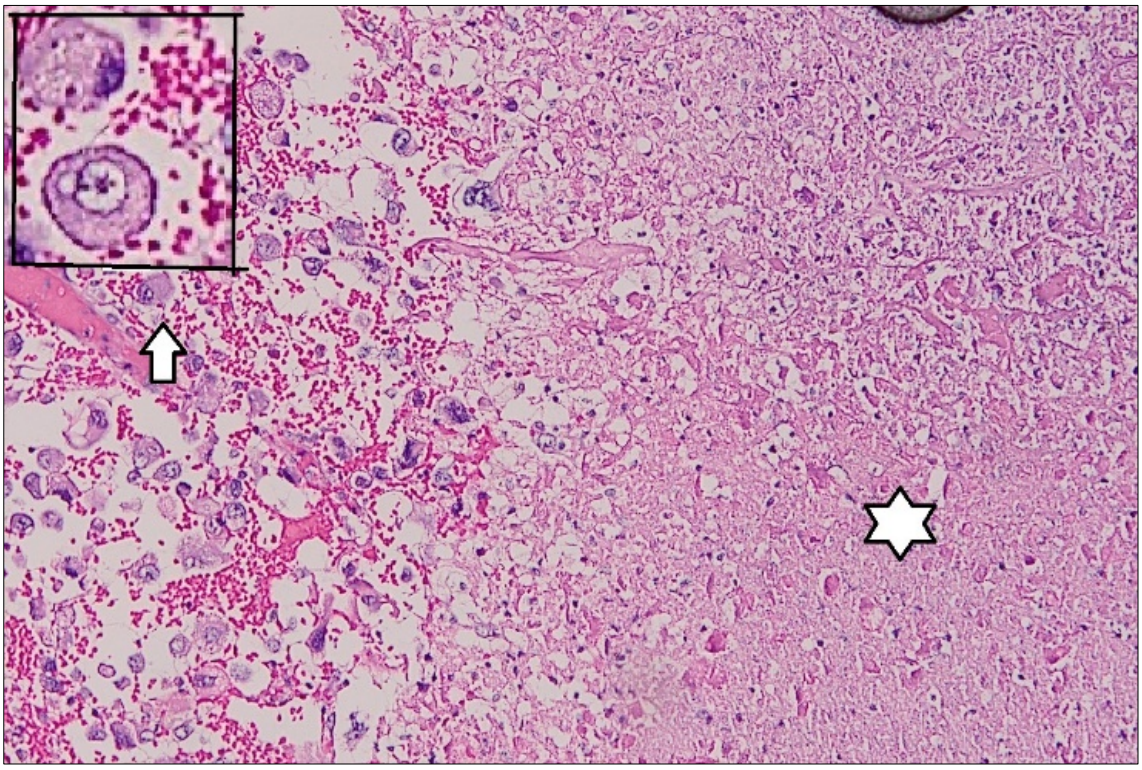

Fig 4

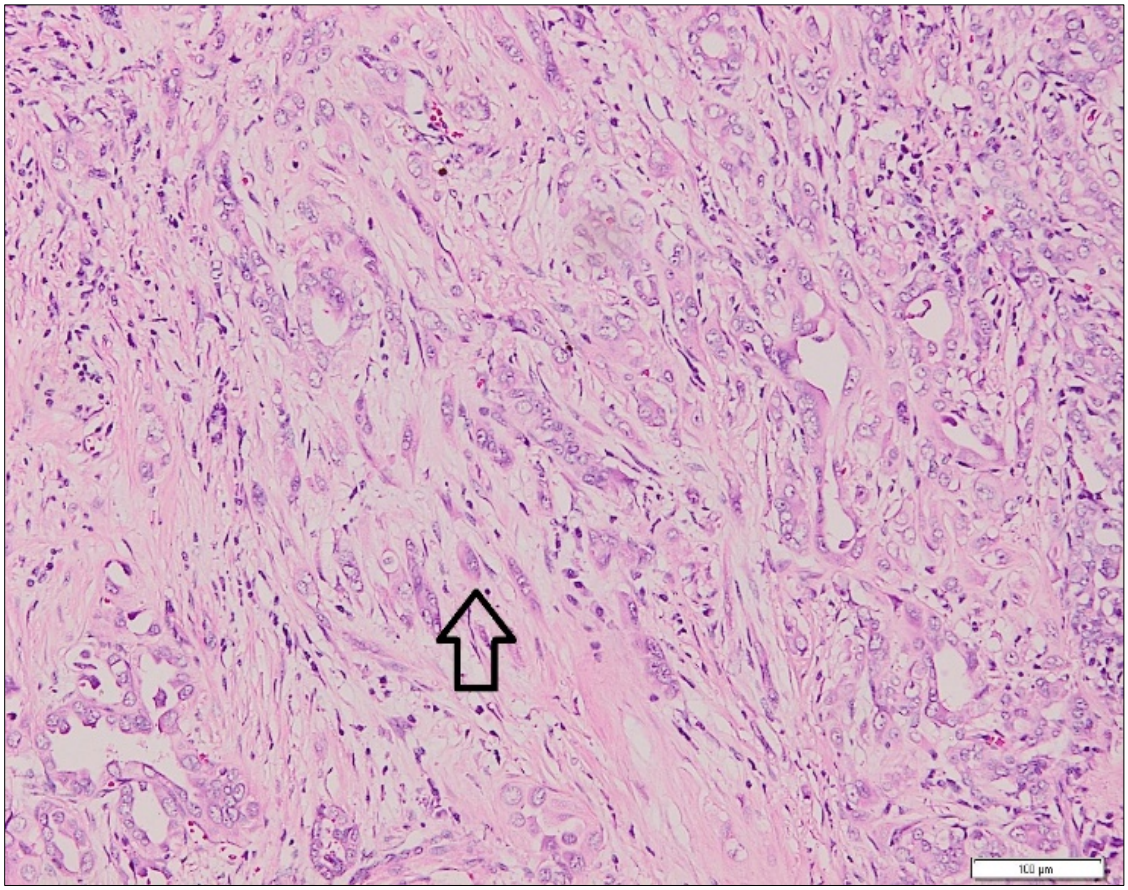

Fig 5

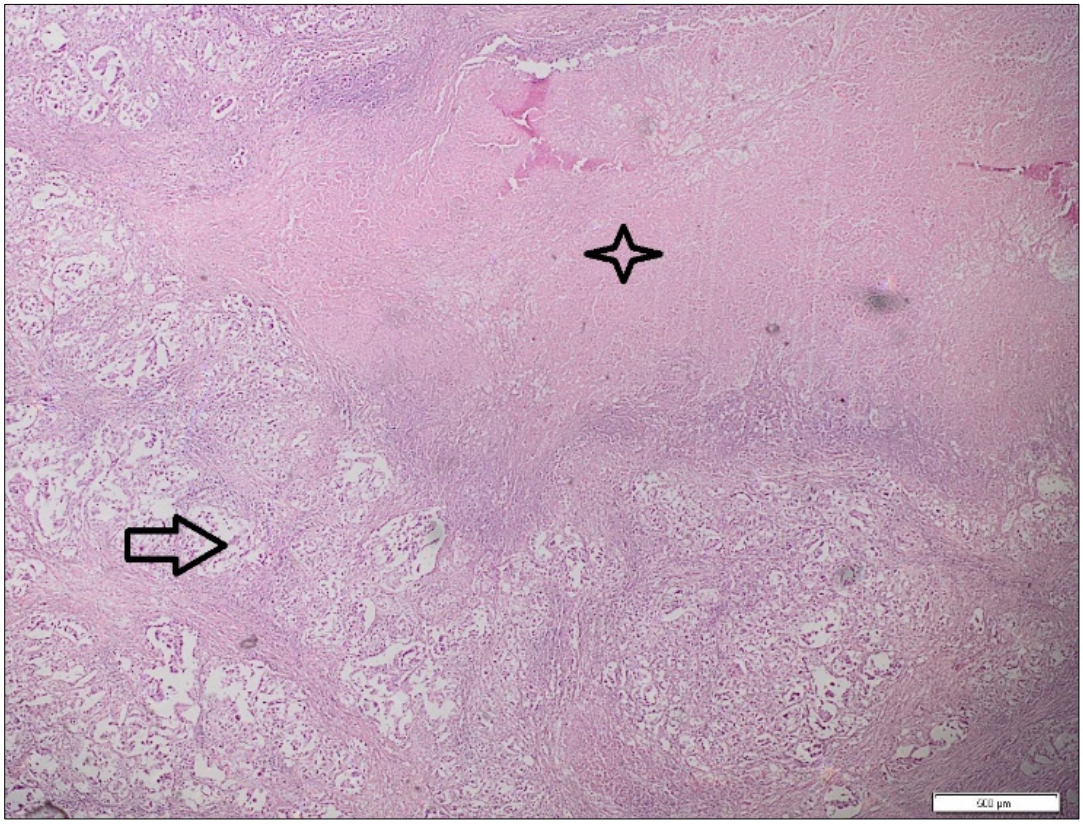

Fig 6

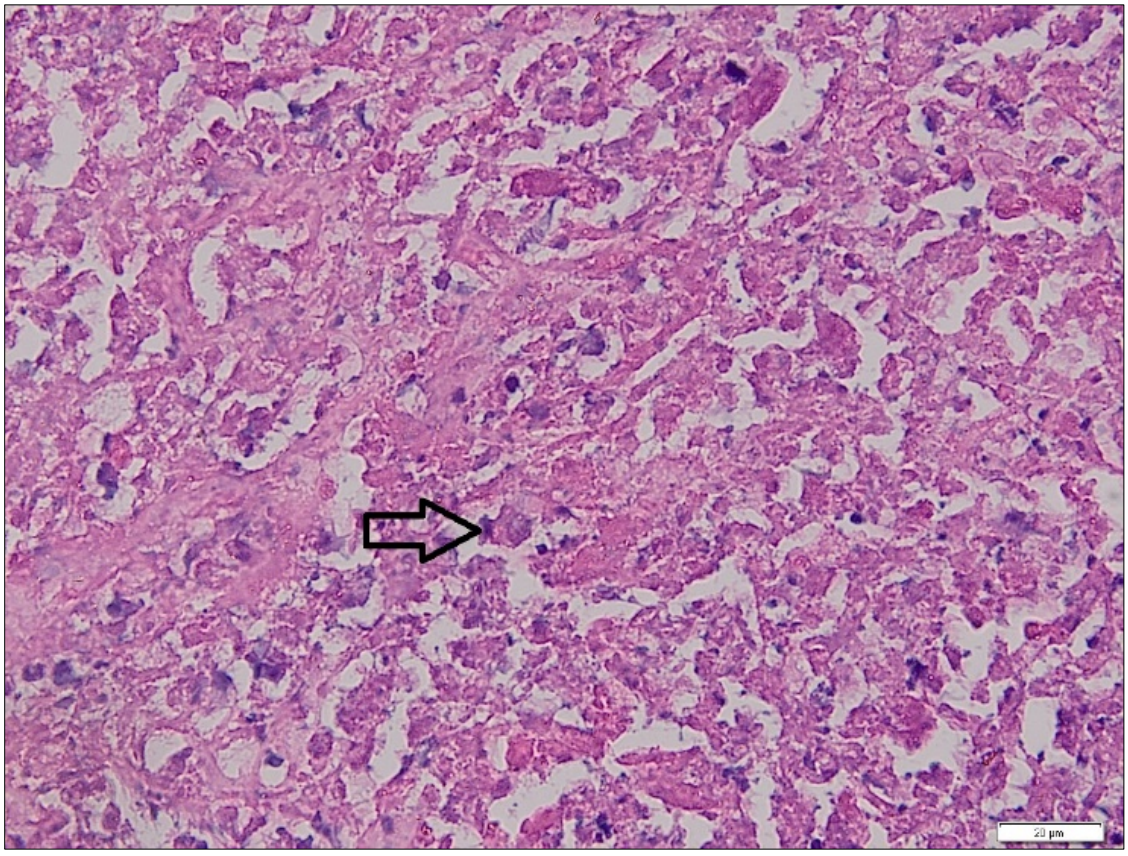

Fig 7

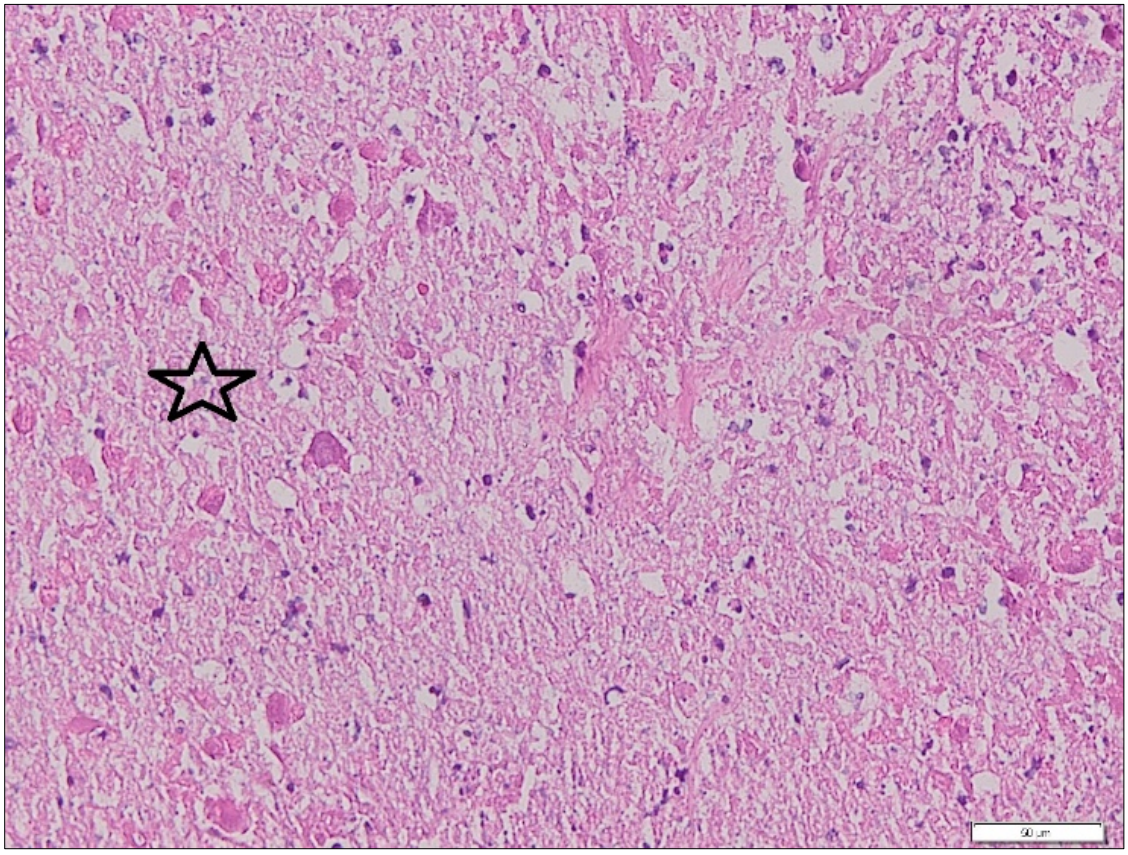

Fig 8

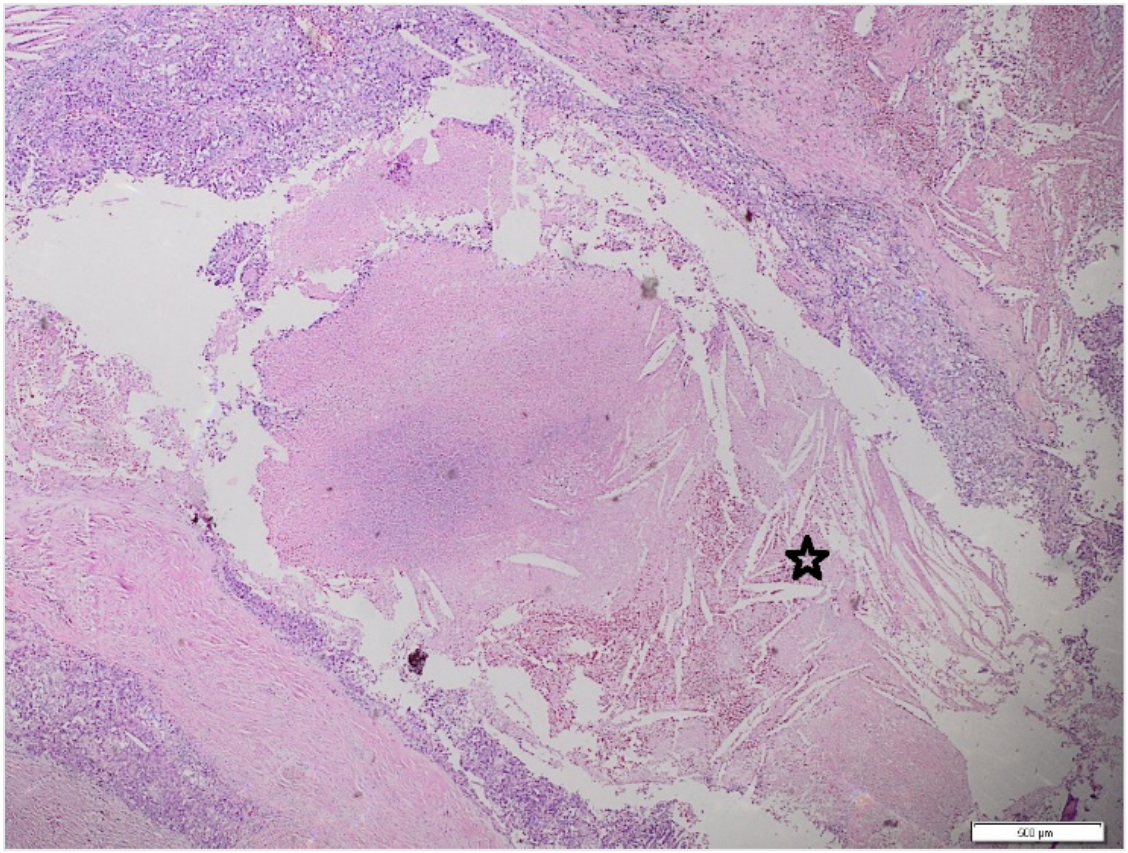

Fig 9

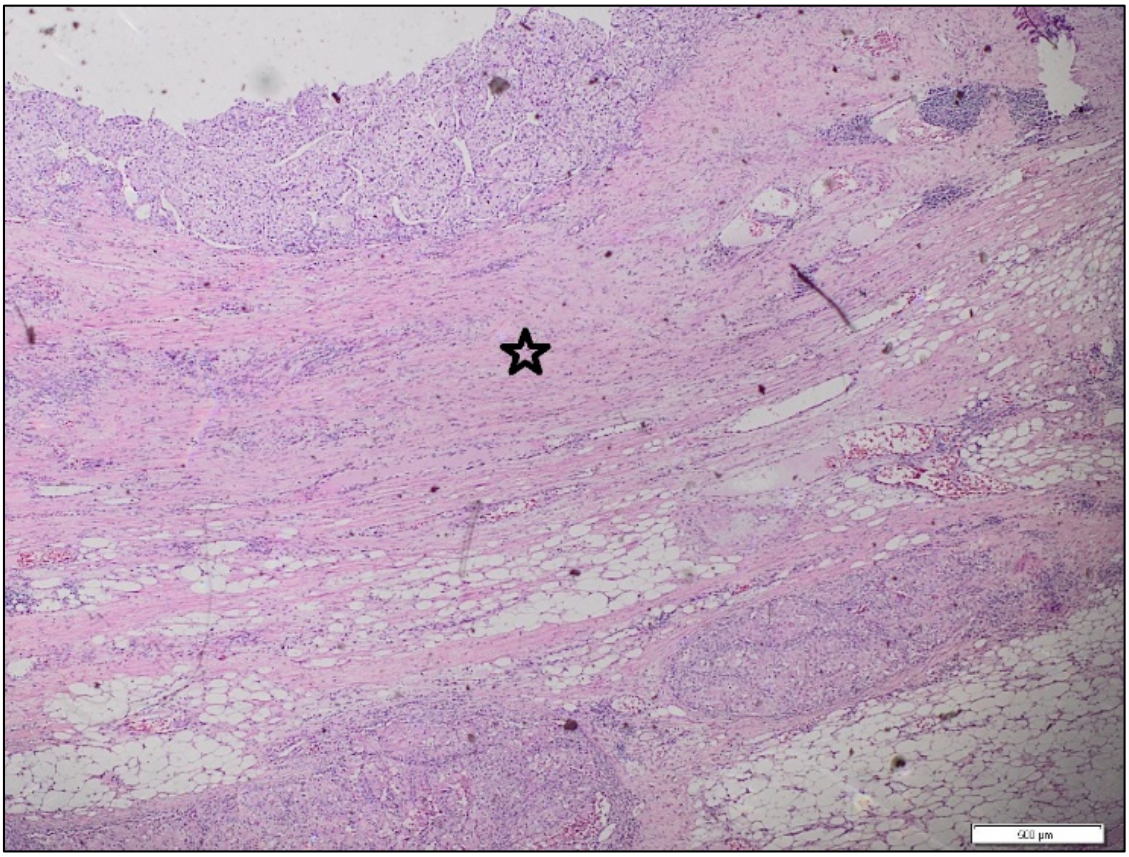

Fig 10

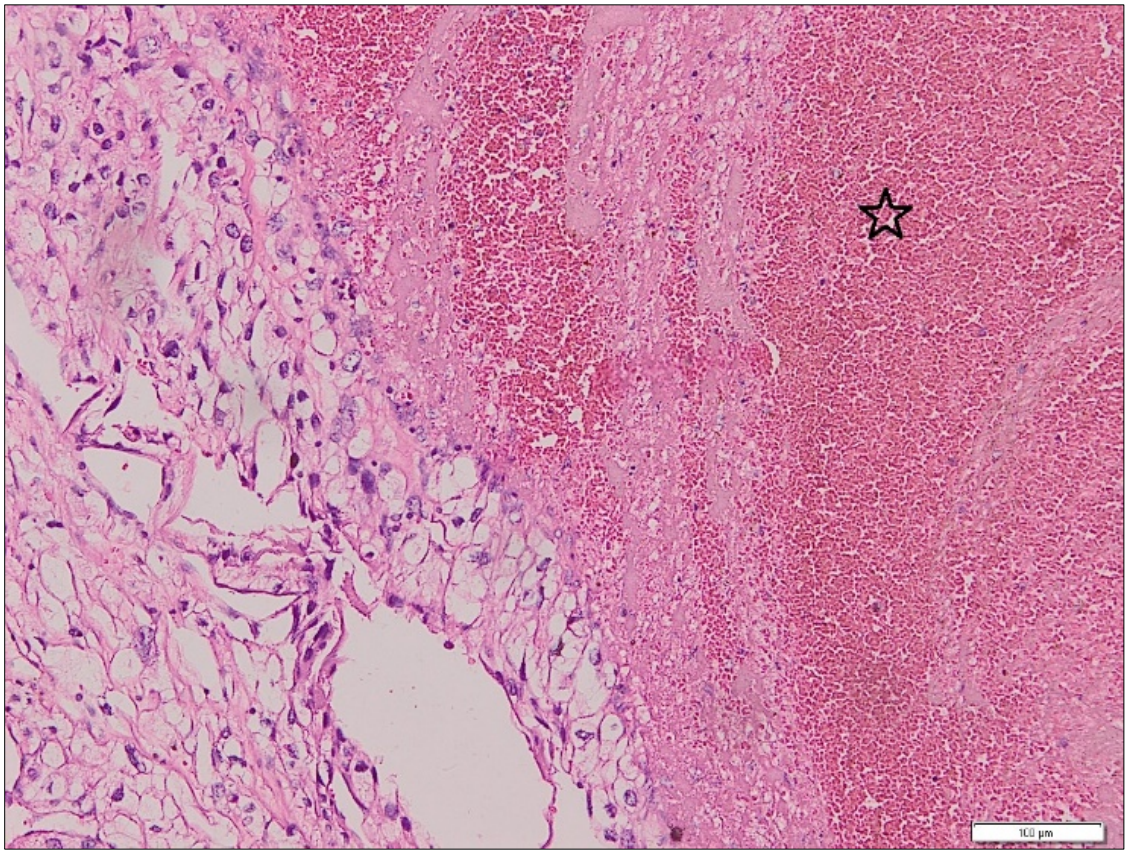

Fig 11

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