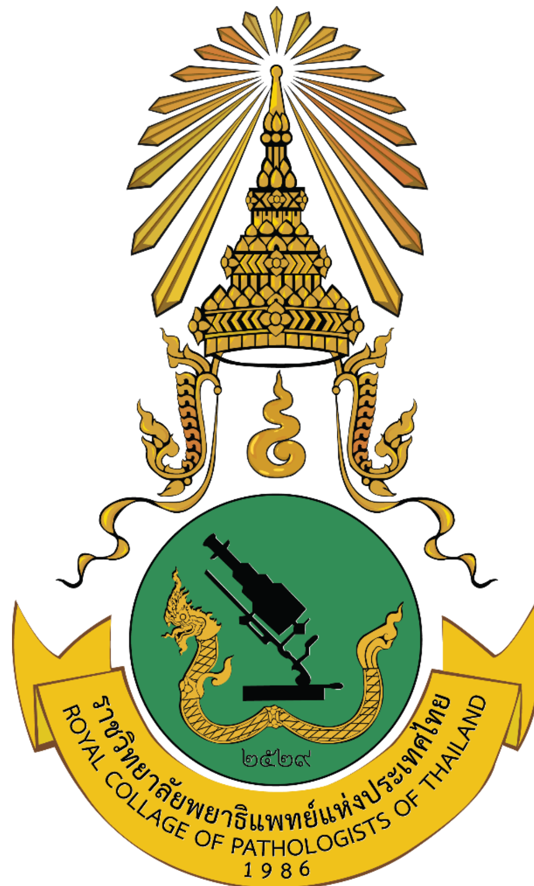
# ASIAN ARCHIVES OF PATHOLOGY

THE OFFICIAL JOURNAL OF THE ROYAL COLLEGE OF PATHOLOGISTS OF THAILAND

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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 "วารสารราชวิทยาลัยพยาธิแพทย์แห่งประเทศไทย" 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) 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**

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## ORIGINAL ARTICLE

# Pathological features of complete and partial hydatidiform mole with usefulness of p57 immunohistochemical stain for the diagnosis

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## Abstract

At Srinagarind Hospital, Khon Kaen, Thailand, the reported proportion of molar pregnancy was 1.28 per 1,000 deliveries or 1:779 deliveries. Many studies show immunohistochemistry for p57 can be used to distinguish complete hydatidiform mole (CHM) from non-CHM. The aim of this study was to find out ratio between CHM and partial hydatidiform mole (PHM) by using p57 immunohistochemistry. Specimens with pathological diagnosis of hydatidiform mole or hydropic chorionic villi from Srinagarind Hospital between January 2012 to March 2019 were recruited. One gynaecologic pathologist, one pathologist and one pathology resident reviewed haematoxylin and eosin (H&E) – stained tissue section slides to confirm the diagnosis. Formalin-fixed, paraffin-embedded tissue sections were stained using a standard immunostaining system with monoclonal antibodies against $p57^{KIP2}$ protein. The pathological features and clinical data were correlated and analysed. Thirty-three hydatidiform mole patients and 13 hydropic abortus patients were enrolled. After consensus review, 24 cases were diagnosed as CHM, 7 cases as PHM, 2 cases as invasive CHM and 13 cases as hydropic abortion. The ratio between CHM and PHM was 3.43:1. In conclusion, the immunohistochemistry for p57 was useful for diagnosis of CHM and PHM.

**Keywords:** gestational trophoblastic disease; hydatidiform mole; $p57^{KIP2}$

## Introduction

Hydatidiform mole (also known as molar pregnancy) is one of gestational trophoblastic diseases and occurs about 1 per 1,000 pregnant women[1]. The prevalence of hydatidiform mole is increased in Asia and middle east[2]. The prevalence of hydatidiform mole at Srinagarind Hospital, Khon Kaen, Thailand is about 1.28 per 1,000 pregnant women[3]. According to the 5$^{th}$ edition of WHO classification tumours of female genital tract, hydatidiform mole is classified into three subtypes: complete hydatidiform mole (CHM), partial hydatidiform mole (PHM) and invasive hydatidiform mole[4]. Sub-classification of hydatidiform mole as CHM and PHM are important for determining the risk of gestational trophoblastic neoplasia (GTN) and clinical management[5]. In the present, mostly cases of hydatidiform mole can be early detected in first trimester of gestation due to standard antenatal care, routine ultrasonography and beta-hCG testing in patient with symptoms of suspicious hydatidiform mole. Many studies show histological overlapping between early CHM and PHM due to lack of classic morphologic features. Additionally, the histopathological appearance can be difficult to distinguish early CHM and PHM by only using routine haematoxylin and eosin (H&E) staining[6,7]. At Srinagarind Hospital, hydatidiform mole is confirmed in H&E – stained tissue sections only. Routine microscopic evaluation without use of ancillary techniques, even in the hands of gynaecologic pathologists and even when a consensus diagnosis was used, demonstrated incorrect classification in at least 20% of cases[8]. The accuracy in subclassification of hydatidiform mole by using routine H&E staining only is 55 – 80% and combined with p57 immunohistochemical staining is 97 – 100%[9]. Many studies show the useful p57$^{KIP2}$ immunohistochemical stain for diagnosis of CHM[10-15]. Molecular genotyping is the gold standard for the diagnosis of CHM, PHM and non-molar abortus, but it is not practically used due to cost-effectiveness. This study was aimed to find out the ratio between CHM and PHM by using p57$^{KIP2}$ immunohistochemistry and to identify epidemiology, clinical course, microscopic features and p57 immunohistochemical stain of hydatidiform mole.

## Materials and Methods

After gaining approval from the Khon Kaen University Ethics Committee for human Research No. 3.4.01:29/2563, patients diagnosed for hydatidiform mole and hydropic abortion at Srinagarind Hospital from January 1, 2012 to March 31, 2019 were reviewed. This study recruited available formalin-fixed, paraffin embedded (FFPE) specimens from hydatidiform mole and hydropic chorionic villi patients. Exclusion criteria consisted of unavailable FFPE

specimens, the remaining specimens less than 1 cm, no available tissue to evaluate immunohistochemistry and loss of medical record. The pool of all hydatidiform moles and hydropic abortions were reviewed. Only eligible cases were enrolled. After we got the patient list, each case was then reviewed microscopically based on the previous official pathological report and H&E – stained glass slides to determine whether it was eligible. The FFPE tissue block was checked whether it was in proper condition to be further processed so if the block was cracked or melt down, it will not be enrolled into the study. The clinical data of the patients was collected based on an outpatient department (OPD) card and an admission record information.

One FFPE tissue block which represented the chorionic trophoblastic lesions with decidual was selected because this type of representative section would provide the data of the hydatidiform mole. Thus, we could properly stain the chorionic trophoblastic lesions and decidual in the same microscopic slide. Three-micron thick tissue sections underwent overnight baking at 50 °C. Deparaffinization and heat pre-treatment antigen retrieval were carried out with Ventana Bench Mark XT®. The bare microscopic glass slide was then stained immunohistochemically by antibody against the $p57^{KIP2}$ protein [Ab-3 (clone KP39), Neomarker, Fremont, CA, USA] at 1:400 dilution and incubated for 32 minutes via automated Ventana Bench Mark XT®. All sections were stained using an autostainer, Ventana Bench Mark XT®. A counterstain was performed by applying one drop of haematoxylin II and subsequently incubating for 20 minutes. Post-counterstain was performed by applying one drop of bluing reagent and incubating for 4 minutes. Decidua and extra-villous trophoblast were served as internal positive control. Appropriate positive and negative controls were run simultaneously.

The stained tissue sections were microscopically examined by one gynaecologic pathologist, one general pathologist and one pathology resident individually. Then, they will be captured throughout the interesting areas into a digital file and saved. Eight features of pathological morphology were evaluated, consisting of hydropic chorionic villi, central cistern, trophoblastic proliferation, atypia of intermediate trophoblast, presence of foetal tissue, two population of chorionic villi, scalloped border and trophoblastic inclusion. Consensus diagnosis was based on H&E – stained slides. The quality of immunohistochemistry was evaluated and interpreted independently by the same three doctors who were blinded from previously histological diagnoses. The $p57^{KIP2}$ expression was evaluated in the nucleus of villous stromal cells and cytotrophoblasts. Positive results were noted when equal or more

than 10% staining of these cells were present and negative results were noted when there was less than 10% staining of these cells.

Clinical characteristics and outcomes of patients were correlated with histologic and immunohistochemical results. Qualitative variables were shown as percentages. Quantitative variables were displayed with median arithmetic and standard deviation. Statistical significance for qualitative variables were analysed with Pearson's correlation using a confidence interval (CI) of 95% ($p$-value < 0.050). Statistical significance for quantitative variables were analysed with the Chi-Square test and Mann-Whitney U test using CI of 95% ($p$-value < 0.050). Sensitivity and specificity were calculated using reviewed histologic diagnosis by H&E stain as gold standard. Statistical analysis was calculated with SPSS version 26.0 (Chicago IL, USA).

## Results

There were 59 cases of hydatidiform mole and hydropic abortus (HA) from January 2012 to March 2020. Thirteen cases were excluded from this study due to loss of FFPE tissue blocks (11 cases), same patient (1 case) and post-chemotherapy (1 case). Total 46 cases were enrolled consisting of 33 cases of hydatidiform mole and 13 cases of hydropic abortus.

Patient characteristics and demographic data were summarised in *Table 1*. The mean age was 32.02 years old. Almost all patients were on first or second pregnancies. The mean gestational age at diagnosis was 11.86 weeks. The most common clinical presentation was abnormal uterine bleeding (65.2%). Median Beta-hCG level was 247,413 mIU/mL. Primary treatment was suction and curettage in most patients (43.5%). This study found 2 cases of invasive CHM at the first presentation and both were treated with chemotherapy and surgery. Three cases of CHM were developed gestational trophoblastic neoplasia (GTN) stage I and both were treated with combination chemotherapy. All patients had successful remission after treatment.

Eight pathological features were evaluated (*Figure 1*). Central cistern, trophoblastic proliferation and atypia of intermediate trophoblast were presented in CHM more often than PHM and significant for CHM ($p$-value < 0.050). Presence of foetal tissue, two populations of chorionic villi, scalloped border and trophoblastic inclusion were presented in PHM more often than CHM and significant for PHM. Hydropic chorionic villi were insignificant features for differentiating CHM from PHM ($p$-value = 1.000). Pathological features and classification of hydatidiform mole and hydropic abortus (HA) are summarised in *Table 2*.

## Table 1 Patient characteristics and demographic data.

| Characteristics | Number of patients | | | | *p*-value |
|---|---|---|---|---|---|
| | Total (N = 46) | CHM (N = 26) | PHM (N = 7) | HA (N = 13) | |
| Age (Years old) (Mean ± SD) | 32.0 ± 8.3 | 31.5 ± 10.4 | 31 ± 5.3 | 33.5 ± 4.3 | 0.033 |
| *< 20* | 2 (4.3%) | 2 (7.7%) | — | — | — |
| *20 – 39* | 35 (76.1%) | 17 (65.4%) | 6 (85.7%) | 12 (92.3%) | 0.227 |
| *≥ 40* | 9 (19.6%) | 7 (26.9%) | 1 (14.3%) | 1 (7.7%) | — |
| Parity | | | | | |
| *Nulliparity* | 19 (41.3%) | 11 (42.3%) | 3 (42.9%) | 5 (38.5%) | 0.961 |
| *Multiparity* | 27 (58.7%) | 15 (57.7%) | 4 (57.1%) | 8 (61.5%) | 0.359 |
| Gestational age (Weeks) at diagnosis (Mean ± SD) | 11.9 ± 4.1 | 11.9 ± 4.8 | 12.7 ± 2.4 | 11.3 ± 3.8 | 0.164 |
| *≤ 12* | 25 (54.3%) | 14 (53.8%) | 3 (42.9%) | 8 (61.5%) | 0.092 |
| *> 12* | 18 (39.1%) | 10 (38.5%) | 4 (57.1%) | 4 (30.8%) | 0.039 |
| Pre-treatment hCG (mIU/mL) (Median) | 247,413 | 299,322 | 43,908 | — | 0.270 |
| Treatment | | | | | |
| *Suction and curettage* | 27 (58.7%) | 23 (88.5%) | 2 (28.6%) | 2 (15.4%) | |
| *Manual vacuum aspiration* | 13 (28.3%) | — | 5 (71.4%) | 8 (61.5%) | |
| *Medical abortion* | 3 (6.5%) | — | — | 3 (23.1%) | |
| *Total abdominal hysterectomy* | 3 (6.5%) | 3 (11.5%) | — | — | |
| Post-molar GTN | 3 (6.5%) | 3 (11.5%) | — | — | — |
| Treatment of post-molar GTN | | | | | |
| *Single CMT* | — | — | | | |
| *Combination CMT* | 3 (100%) | 3 (100%) | | | |
| *Surgery* | — | — | | | |

***Note:*** *CHM = Complete hydatidiform mole; GTN = Gestational trophoblastic neoplasia; HA = Hydropic abortus; PHM = Partial hydatidiform mole; and SD = Standard deviation*

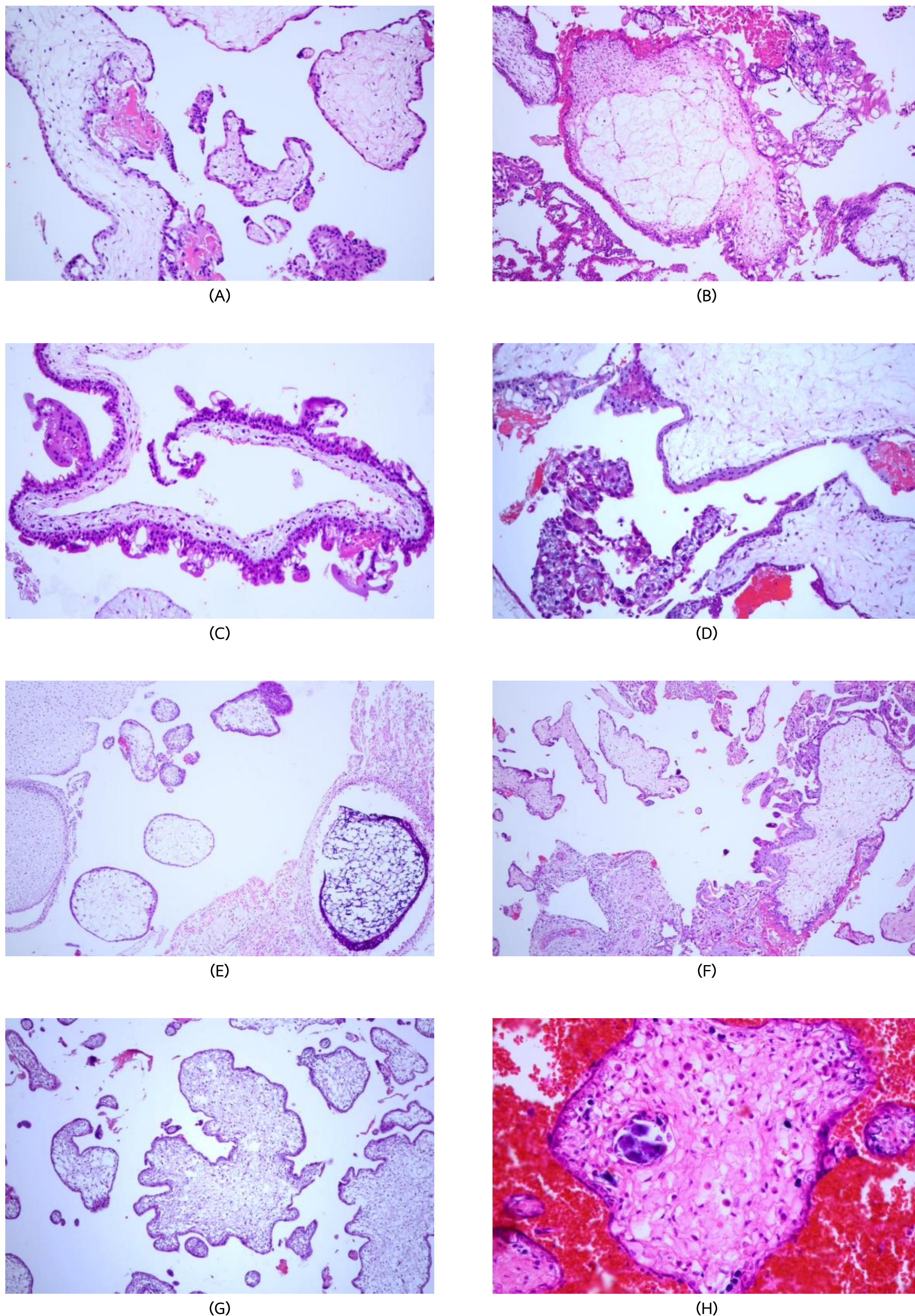


**Figure 1 Pathological features of hydatidiform mole and hydropic abortus (H&E stain). (A).** Hydropic chorionic villi (100x magnification); **(B).** Central cistern (40x magnification); **(C).** Trophoblastic proliferation (100x magnification); **(D).** Atypia of intermediate trophoblast (100x magnification); **(E).** Presence of foetal tissue (40x magnification); **(F).** Two population of chorionic villi (40x magnification); **(G).** Scalloped border (40x magnification); and **(H).** Trophoblastic inclusion (200x magnification).

Table 2 Pathological features between hydatidiform mole and hydropic abortus.

| Diagnosis | Pathologic features (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Hydropic villi | Central cistern | Trophoblastic proliferation | Atypia of intermediate trophoblast | Presence of foetal tissue | Two population of villi | Scalloped border | Trophoblastic inclusion |
| CHM | 100 | 100 | 100 | 92.3 | 0 | 0 | 57.7 | 23.1 |
| PHM | 100 | 14.3 | 71.4 | 28.6 | 57.1 | 85.7 | 100 | 85.7 |
| HA | 100 | 0 | 30.8 | 0 | 0 | 0 | 7.7 | 0 |
| *p*-value | 1.000 | < 0.010 | < 0.010 | < 0.010 | < 0.010 | < 0.010 | 0.038 | < 0.010 |

***Note:*** *CHM = Complete hydatidiform mole; HA = Hydropic abortus; and PHM = Partial hydatidiform mole*

After 46 cases were histologically reviewed. A total of 46 cases were classified at first diagnosis, i.e. 20 cases of CHM, 7 cases of PHM, 2 cases of invasive CHM, 2 cases of unspecified hydatidiform mole, 14 cases of HA and 1 case of unspecified PHM or HA. H&E stain was gold standard for diagnosis in this study. Sensitivity of the first diagnosis by H&E for CHM and PHM were 80.77% and 71.43%, respectively. Specificity of the first diagnosis by H&E for CHM and PHM were 95% and 94.87%, respectively. Final diagnosis was reached by consensus of one gynaecologic pathologist, one general pathologist and one resident of pathology, i.e. 24 cases of CHM, 7 cases of PHM, 2 cases of invasive CHM and 13 cases of HA. Discordant diagnosis between the first and final diagnosis by H&E stain was found in 7 cases (15.22%) [2 cases from unspecified hydatidiform mole (HM) to CHM, 2 cases from PHM to CHM, 1 case from CHM to PHM, 1 case from PHM or HA to PHM and 1 case from HA to CHM.

Following immunohistochemistry (IHC) staining for $p57^{KIP2}$ (*Figure 2*), discordant diagnosis between histopathology and $p57^{KIP2}$ was identified in 1 case (2.17%). One case of $p57^{KIP2}$ – positive CHM was reclassified as PHM (*Table 3*). The ratio between CHM and PHM was 3.43:1. Based on the final diagnosis by H&E stain with p57 immunohistochemistry for CHM and PHM, sensitivity was 100% and 85.71%, respectively. Specificity was 95% and 100%, respectively.

## Discussion

Sub-classification of hydatidiform mole was associated with the risk of postmolar GTN and clinical management. In this study, the ratio between CHM and PHM was 3.43:1. Generally, the incidence of hydatidiform mole, especially CHM, is higher in Asia than other regions of the world. Postmolar GTN were identified in 3 cases from this study which all cases were negative $p57^{KIP2}$. Although patients with both CHM and PHM should be monitored with serial beta-hCG, accurate sub-classification of hydatidiform mole is important to determine the actual risk of GTN and to correct disease prognosis.

The diagnosis and subclassification of hydatidiform mole are based on pathologic features. In this study, the significant pathologic features for CHM were central cistern, trophoblastic proliferation and atypia of intermediate trophoblast, and the significant pathologic features for PHM were presence of foetal tissue, two populations of chorionic villi, scalloped border and trophoblastic inclusion. Whereas hydropic chorionic villi were insignificant for distinguishing between hydatidiform mole from HA. However, histological criteria for distinguishing between CHM and PHM are subjective and difficult to reproducible. The pathological features can be presented in both CHM and PHM, especially in the first

trimester of gestation such as central cavitation, non-circumferential trophoblastic proliferation, mild atypia of intermediate trophoblast, presence of foetal blood vessels, mild irregular villous contour or scalloped border and trophoblastic inclusion due to lesser gestational age leads to a more incomplete development of typical molar morphology. In the present, we can diagnose hydatidiform mole at an earlier gestational age, compared to previous decades. In addition, criteria for diagnosis in early CHM overlap with PHM include minimal villous cavitation, mild hydropic chorionic villi, presence of foetal blood vessels, irregular villous and villous pseudo-inclusion. In this study, one case was histologically diagnosed as early CHM but revealed positive results for $p57^{KIP2}$.

The *$p57^{KIP2}$* is a cyclin-dependent kinase inhibitor located at the chromosome locus 11p15.5. Previous studies found *$p57^{KIP2}$* related to several human malignancies[16]. The $p57^{KIP2}$ immunohistochemistry is one of the tools to distinguish CHM from non-CHM[17,18]. The discordant diagnosis between histopathology and $p57^{KIP2}$ was 2.17% which was comparable to 4.4 – 15% from other studies[14,15,19]. Comparing with $p57^{KIP2}$, sensitivity and specificity of diagnosis by H&E for CHM in our study were 80.77% and 95%, respectively and lower than results from Triratanachat et al (89.7% and 95%)[15].

Immunohistochemistry for $p57^{KIP2}$ is rapid, practical and cost-effective, and should be utilised to distinguish CHM from non-CHM in every case of suspected hydatidiform mole[20-22]. According to this study, immunohistochemistry for p57 should be used in the general practice for diagnosis CHM and PHM. There is a limitation of this study due to small population and lack of genomic study in p57-positive CHM. The case of CHM with positive $p57^{KIP2}$ should be performed additional ploidy analysis for the definite diagnosis. Although immunohistochemistry for $p57^{KIP2}$ is usually positive in PHM and non-molar hydropic gestations, it is also positive in CHM with retained maternal chromosome 11 and mosaic androgenetic/chimeric gestations. Immunohistochemistry for $p57^{KIP2}$ is usually negative in CHM and it is also negative in PHM with loss of maternal chromosome 11[23].

Additional genomic study such as ploidy analysis, short tandem repeat genotyping should be performed in inconclusive pathological diagnosis[24]. Short tandem repeat DNA genotyping provides precise diagnosis for PHM by identifying diandric triploidy and for CHM by identifying the absence of maternal genetic contribution (androgenetic-only genome).

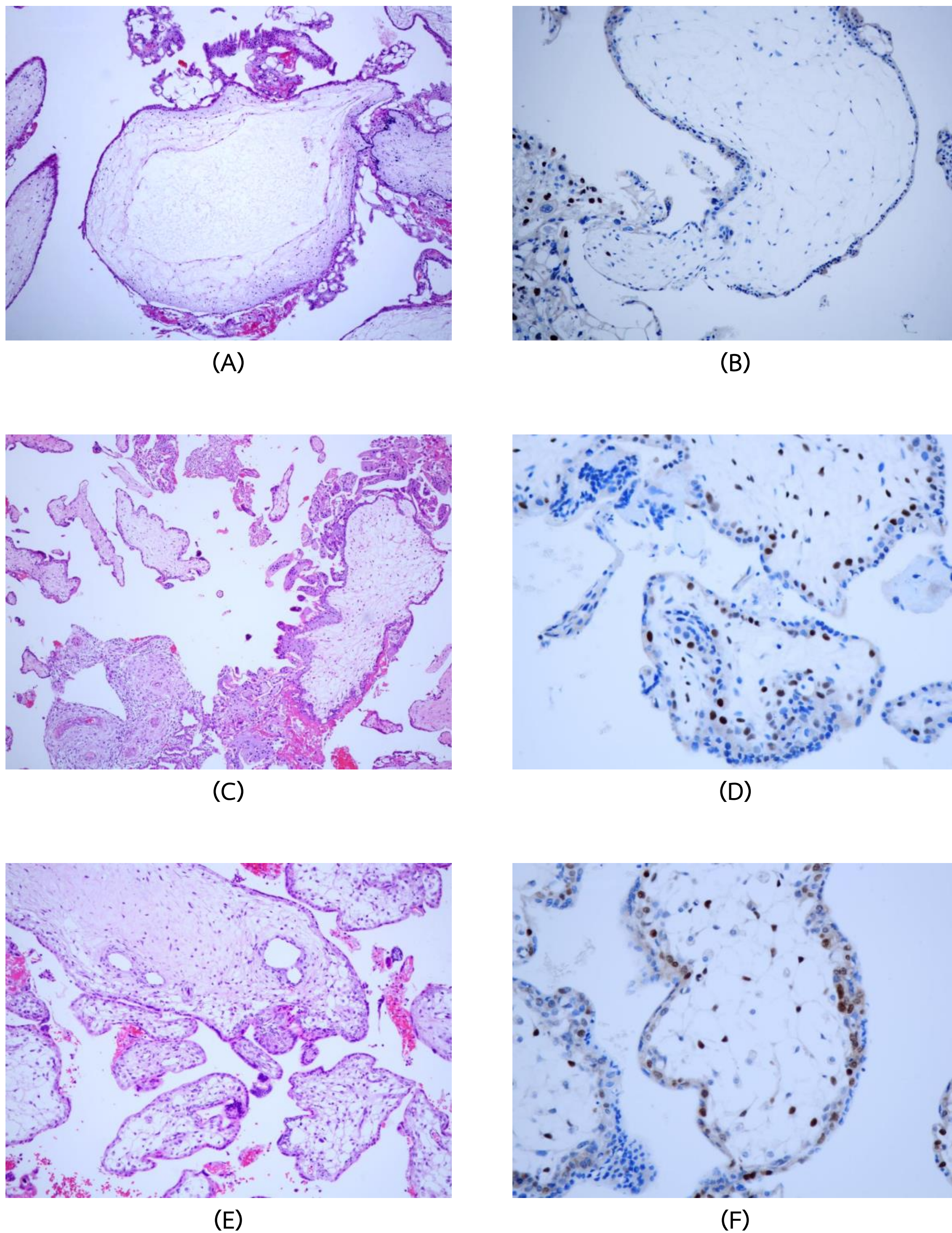


**Figure 2 Immunohistochemistry of p57 in hydatidiform mole and hydropic abortus.** Complete hydatidiform mole: **(A).** H&E stain (40x magnification) and **(B).** p57 immunoexpression (100x magnification). Partial hydatidiform mole: **(C).** H&E stain (40x magnification) and **(D).** p57 immunoexpression (200x magnification). Hydropic abortus: **(E).** H&E stain (100x magnification) and **(F).** p57 immunoexpression (200x magnification).

Table 3 Histologic diagnosis and p57 immunostaining.

| Diagnosis | First histologic diagnosis | Reviewed diagnosis by H&E stain only | Final diagnosis by H&E stain with p57 immunoexpression |
|---|---|---|---|
| CHM | 20 | 25 | 24 |
| Invasive CHM | 2 | 2 | 2 |
| PHM | 7 | 6 | 7 |
| HA | 14 | 13 | 13 |
| PHM or HA | 1 | 0 | 0 |
| Unspecified HM | 2 | 0 | 0 |
| Total | 46 | 46 | 46 |

***Note:*** *CHM = Complete hydatidiform mole; HA = Hydropic abortus; HM = Hydatidiform mole and PHM = Partial hydatidiform mole*

## Conclusion

The immunohistochemistry of $p57^{KIP2}$ is useful for supporting the diagnosis of CHM, especially in early gestational age, but cannot distinguish PHM and HA. Additional genomic study such as ploidy analysis, short tandem repeat genotyping should be performed in inconclusive cases.

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## ORIGINAL ARTICLE

# Viral studies in autopsies of foetal death *in utero* at Srinagarind Hospital, Khon Kaen University

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## Abstract

Foetal autopsy cannot find the cause of foetal death in all cases. Viral infections may be a cause of foetal death. PCR can be used to detect viral DNA. This study was to determine prevalence of CMV, HSV, parvovirus B19 and HHV-6 by using PCR in autopsies of foetal death *in utero*. A retrospective study of autopsies of foetal death in utero in the Department of Pathology at Srinagarind Hospital between 1 April 2019 and 30 August 2020 was performed. Each case was histopathologically examined for evidence of infection. Ninety-five percent of ethanol fixed foetal heart, lungs, liver and placenta tissues were used for PCR for viral DNA. Autopsy findings and clinical data were analysed. Thirty-six cases of foetal death *in utero* were enrolled. Approximately 31% of cases were positive for parvovirus B19. Other viral PCRs were negative. Spontaneous foetal death and termination of pregnancy groups differed in the detection rate of parvovirus B19 (35.0% and 25.0%). Autopsy findings between PCR-positive and PCR-negative groups showed no significantly statistical differences in hydrops foetalis (18.1% and 4%). In conclusion, the prevalence of parvovirus B19 infection in foetal death *in utero* at Srinagarind Hospital is higher than the previous report.


**Keywords:** cytomegalovirus; foetal death; human herpesvirus 6; herpes simplex virus; parvovirus B19

## Introduction

Foetal autopsies cannot find causes of foetal death in utero all cases. A previous study in autopsies of dead foetuses in Srinagarind Hospital, Khon Kaen University found unexplained causes of 22%[1]. Intrauterine viral infections can be a cause of foetal death in 25 – 38% of unexplained foetal death[2]. Most common intrauterine viral infections were cytomegalovirus (CMV) (63%), parvovirus B19 (33%) and herpes simplex virus (41%). Herpes simplex virus was only detected in neonatal death[3]. Foetal death in utero and stillbirth infants in pregnant women who have pityriasis rosea that were infected by human herpesvirus-6 (HHV-6) also were detected by finding HHV-6 DNA in placentas and foetal tissues[4]. Previous studies showed detection of viral DNA in foetal tissues higher than expected[5,6]. In this present study, the PCR methods to detect CMV, HSV, parvovirus B16 and HHV-6 DNAs were used. Autopsy findings and histopathology were also studied.

## Materials and Methods

### Population:

The Centre for Ethics in Human Research, Khon Kaen University approved this study (HE641021). Thirty-six specimens of foetal death *in utero* were performed at autopsy in the Department of Pathology, Srinagarind Hospital, Khon Kaen University, Thailand between 1 April 2019 and 30 August 2020. Foetal death *in utero* (DFIU) was defined as the intrauterine death of a foetus at any time during pregnancy. All cases of foetal death were aborted or delivered in the Department of Obstetrics and Gynaecology, Srinagarind Hospital, Khon Kaen University. Consent for autopsy was given for autopsy by the parents of the foetus. Gestational age of the dead foetuses in this study ranged from 18 to 39 weeks. The foetuses that could not be completely autopsied such as in severe maceration with liquidising of internal organs or the parents who did not give consent were excluded from this study. Maternal obstetric histories were evaluated, i.e. maternal age, maternal underlying diseases, history of labour, ultrasound findings and infectious signs such as fever and results from the microbiology laboratory. Forty-two cases of foetal death *in utero* were autopsied but only 36 cases are included in this study. Six cases were excluded because they had severe maceration with liquidising internal organs in that tissue samples were not for the study.

### Autopsy examinations:

All 36 foetuses with placentas were autopsied. Placentas of 3 cases were not obtained. Congenital anomalies were recorded. In autopsy, small pieces of dead foetal tissues of heart,

liver, lungs and placenta were sampled and fixed in 95% ethanol. The alcohol-fixed foetal tissues were stored at -80 °C. The foetal tissues were also fixed in formalin, embedded in paraffin and processed to haematoxylin and eosin (H&E) slides. Histological examination was performed. Neutrophilic infiltration of membranes and chorionic plates were defined as acute chorioamnionitis.

**DNA extraction and polymerase chain reaction (PCR):**

Ninety-five percent alcohol fixed foetal tissues, i.e. heart, liver, lung and placenta tissues, were collected from 36 dead foetuses. DNA was extracted from each tissue sample by using Omega Bio-tek EZNA® Tissue DNA Kits. Extractions were aliquoted and stored at -80 °C until used. A multiplex nested PCR method was used for CMV and HSV-1 & -2 detection[7]. The primers used in a multiplex nested PCR reaction included 1) the first-round primers; HCMV-Sense1, AAGGTCATCTACGGGGACACGGA, HCMV-Antisense1, ACTTTGCCGATGTAACGTTTCTT, HSV-Sense1, CGCATCATCTACGGGGACACGGA and HSV-Antisense1, ATGACGCCGATGTACTTTTTCTT and 2) the second-round primers were; HCMV-Sense2, GGGCCCAGCCTGGCGCACTA, HCMV-Antisense2, GACGAAGACCTTTTCAAACTC, HSV-Sense2, GTGTTGTGCCGCGGTCTCAC and HSV-Antisense2, GGTGAACGTCTTTTCGAACTC. The extracted DNA was mixed into a 25 µL mastermix containing: 2.5 µL of 10x buffer, 4.0 µL of 25 mM MgCl2, 0.5 µL of 10 mM dNTPs, 0.5 µL of 10 µM HSV-Sense1, 0.5 µL of 10 µM HSV-Antisense1, 0.5 µL of 10 µM HCMV-Sense1, 0.5 µL of 10 µM HCMV-Antisense1, 0.125 µL of Taq polymerase, 13.875 µL of sterile distilled water and 2.0 µL of DNA sample (100 ng/reaction). Amplifications of multiplex-nested PCR were performed with the following parameters; initial denaturing at 95 °C for 5 minutes, 40 cycles comprised of 95 °C for 30 seconds, 52 °C for 1 minute with first round primers or 47 °C for 1 minute with second round primers, and 72 °C for 3 minutes and a final extension step at 72 °C for 10 minutes. The nested PCR method was used for parvovirus B19 detection[5]; The first-round primers were Prm4a, AACGCCTCAGAAAAATACCC and Prm4b, TAAGTGCTGAAACTCTAAAGG. The second-round primers were B19-1, CAAAAGCATGTGGAGTGAGG and B19-2, ACCTTATAATGGTGCTCTGGG. The extracted DNA was mixed into a 25 µL master-mix containing: 2.5 µL of 10x buffer, 4.0 µL of 25 mM MgCl2, 0.5 µL of 10 mM dNTPs, 0.5 µL of 10 µM of forward primer, 0.5 µL of 10 µM of reverse primer, 0.125 µL of Taq polymerase, 14.875 µL of sterile distilled water and 2.0 µL of DNA sample (100 ng/reaction). Amplifications of the first and second round were performed with the following parameters; initial denaturing at 94°C for 7 minutes, 40 cycles comprised of 94°C for 30 seconds, 55°C for 30 seconds, 72°C for 30 seconds and a final extension step at 72°C for 5

minutes. The PCR products of CMV, HSV-1 & -2 and parvovirus B19 were subjected to electrophoresis on 1.5% agarose gel for the first round PCR product and 2.0 % agarose gel for the second round PCR product and visualised by ethidium bromide staining. The conventional PCR method was used for HHV-6 detection(8). The extracted DNA was mixed into a 25 µL mastermix containing: 2.5 µL of 10x buffer, 4.0 µL of 25 mM MgCl2, 0.5 µL of 10 mM dNTPs, 0.625 µL of 10 µM of forward primer, 0.625 µL of 10 µM of reverse primer, 0.125 µL of Taq polymerase, 14.625 µL of sterile distilled water and 2.0 µL of DNA sample (100 ng/reaction). The primers were U67 HHV 6 Int-F, GCTAGAACGTATTTGCTGCAGAACG and U67 HHV-6 Int-R, ATCCGAAACAACTGTCTGACTGGCA. Amplifications were performed with the following parameters; initial denaturing at 95 °C for 3 minutes, 35 cycles comprised of 95 °C for 45 seconds, 56 °C for 45 seconds, 72 °C for 45 seconds and a final extension step at 72 °C for 5 minutes. The PCR products of HHV-6 were subjected to electrophoresis on 1.5% agarose gel and visualised by ethidium bromide staining. Tissues that are known to be positive CMV, HSV-1 & -2, parvovirus B19 and HHV-6 were used as positive controls. *Glyceraldehyde 3-phosphate dehydrogenase (GAPDH)* gene was used as the internal control(9).

**Statistical analysis:**

The descriptive results were shown as means. For comparison between study groups, the Fisher Exact was used. P-values of < 0.05 were considered statistically significant. Analysis was performed using statistical SPSS 26 software.

## Results

**Demographic data:**

A total 36 cases of death foetal *in utero* that consisted of 20 cases of spontaneous abortion or delivery and 16 cases of termination of pregnancy were autopsied. The mean gestational age was 26.4 weeks. Twenty-one cases were of gestational ages of at least 24 weeks. Fifteen cases were of gestational ages of less than 24 weeks. Fourteen foetuses were male and 21 foetuses were female. One case was of ambiguous genitalia. The mean weight was 1,102.7 grams (*Table 1*). Maternal VDRL tests were done in 8 cases and were positive in 2 cases. TORCH titers were tested in 3 cases and all were negative for acute infection.

**Table 1 Demographic data.**

| Characteristics | Number of patients |
|---|---|
| Age of mothers (Years old) | |
| *< 20* | 4 (11.1%) |
| *20 – 35* | 27 (75.0%) |
| *> 35* | 5 (13.9%) |
| Mean maternal age (Years old) | 29.55 |
| Gestational age (Weeks) | |
| *< 24* | 15 (41.6%) |
| *24 – 37* | 19 (52.8%) |
| *> 37* | 2 (5.6%) |
| Mean gestational age (Weeks) | 26.4 |
| Sex of foetuses | |
| *Female* | 21 (58.3%) |
| *Male* | 14 (38.9%) |
| *Unidentified* | 1 (2.8%) |
| Foetal weight (Grams) | |
| *< 500* | 12 (33.3%) |
| *≥ 500* | 24 (66.7%) |
| Mean foetal weight (Grams) | 1,102.7 |

**Detections of viral DNA:**

Thirty-six cases of examined foetal death tissues consisted of 36 heart tissues, 36 liver tissues, 36 lung tissues and 33 placental tissues. Eleven out of 36 (30.6%) cases were positive for parvovirus B19. In the spontaneous abortion or delivery group, 7 cases were positive for parvovirus B19 (35% of the spontaneous abortion or delivery group). In the termination of pregnancy group, 4 cases were positive for parvovirus (25% of termination of pregnancy group). Spontaneous foetal death (35.0%) and termination of pregnancy groups (25%) differed in the detection rate of parvovirus B19, but were not statistically different (*p*-value = 0.7182). Seven out of 21 (33.3%) foetuses of gestational age of at least 24 weeks were positive for parvovirus. Four out of 14 (26.7%) fetuses of gestational age of less than 24 weeks were positive for parvovirus. The difference for parvovirus detection between the 2 groups was not significant

(*p*-value = 0.7288). Mean gestational ages of parvovirus-positive group and parvovirus-negative group were 27.6 weeks and 25.9 weeks, respectively. The mean gestational ages did not differ between groups of parvovirus-positive and -negative (*p*-value = 0.46). Parvovirus B19 was detected in 5 liver tissues, 4 heart tissues, 4 placenta tissue and 2 lung tissues (*Tables 2 – 3*).

**Table 2 Comparison of parvovirus B19 detection between spontaneous abortion and termination of pregnancy.**

| Case | Parvovirus B19 detection | | | *p*-value |
|---|---|---|---|---|
| | Positive | Negative | Total | |
| Spontaneous abortion | 7 (35%) | 13 (65%) | **20 (55.56%)** | 0.72 |
| Termination of pregnancy | 4 (25%) | 12 (75%) | **16 (44.44%)** | |
| **Total** | **11 (30.56%)** | **25 (69.44%)** | **36 (100%)** | |

**Table 3 Comparison of parvovirus B19 detection between hydrops foetalis and non-hydrops foetalis**.

| PCR for parvovirus B19 detection | Hydrops foetalis | Non-hydrops foetalis | Total | *p*-value |
|---|---|---|---|---|
| Positive | 2 (18.2%) | 9 (81.8%) | **11 (32.35%)** | 0.22 |
| Negative | 1 (4.4%) | 22 (95.6%) | **23 (67.65%)** | |
| **Total** | **3 (8.82%)** | **31 (91.18%)** | **34 (100%)** | |

**Autopsy and histologic findings:**

Five cases of hydrops foetalis were autopsied and the gestational ages ranged from 19 to 33 weeks. One case was cystic hygroma and 1 case was Bart's hydrops foetalis. In 3 cases of hydrops foetalis, the cause of hydrops foetalis was not found. After excluding 2 cases that were known to be the causes of hydrops foetalis, the differences in hydrops foetalis (18.2% and 4.5%) between PCR-positive and PCR-negative groups were not statistically significant (*p*-value = 0.22) (*Figures 1 – 2*). Four cases had acute chorioamnionitis and all were negative for parvovirus B19. Among 4 cases of acute chorioamnionitis, 2 cases had maternal syphilis.

Congenital abnormalities including neurological defects, cardiovascular defects, GI tract anomalies, extremity anomalies and foetal hepatoblastoma were found in 16 (44.4%) cases. Congenital abnormalities did not differ between parvovirus B19 – positive and – negative foetuses ($p$-value = 0.16) (*Tables 4 – 5*).

## Discussion

Previous studies reported viral DNA detection rates in foetal death *in utero* as CMV (16 – 27.4%), HSV (2.8 – 6.8%), parvovirus B19 (6.8 – 13%) and HHV-6 2.7%[5,6]. In this study, the overall detection rate of parvovirus B19 DNA in foetal death in utero was 30.6% (95% CI 15.5 – 45.6%), higher when compared the previous studies and not detected for CMV, HSV and HHV-6 DNA. In Thailand, there are few studies about the incidence of parvovirus B19. Bhattarakosol et al studied the prevalence of antibody to human parvovirus B19 in Thai young adults and reported 10.94% IgG seropositive for parvovirus B19[10]. For the other viruses, there are only seroepidemiology studies that cannot compare directly to this study. The difference of viral DNA detection between this study and previous studies could be explained as this study used fresh tissue for PCR that was slightly better quality than formalin-fixed, paraffin-embedded tissue. The parvovirus B19 DNA detection rate was not related to gestational age, similar to the previous study. Congenital abnormalities were detected similarly between the parvovirus B19 – positive and – negative groups. This is the same finding as the previous study. Chorioamnionitis did not differ between the parvovirus B19 – positive and – negative groups, similar to the previous study. Parvovirus B19 positive (18.1%) and Parvovirus B19 negative (4%) groups differed in hydrops foetalis, but were not statistically different in contrast to the previous report where the difference of hydrops foetalis was statistically significant between the two groups[11]. Most of the previous studies reported that the hydrops foetalis was the most common finding. Viral inclusion is also reported but it is rare. The difference could be explained as this study had a small sample size. This study used alcohol-fixed foetal tissues that is slightly superior to formalin-fixed tissue for DNA extraction and PCR[12]. Further study should have a larger sample size. The high prevalence of parvovirus B19 DNA detection rate suggests foetal death *in utero* especially in hydrops foetalis should promote screening tests for parvovirus B19 both in the mother and foetus.

Table 4 Autopsy findings in spontaneous abortion cases.

| Case number | Sex | Gestational age (Weeks) | Organ | Autopsy data | Viral PCR |
|---|---|---|---|---|---|
| 1 | M | 38 | H, Liv, L | Cause unknown | Neg |
| 2 | F | 25 | H, Liv, L, **P** | Abruptio placenta with placental insufficiency | PVB 19 |
| 3 | F | 36 | H, Liv, L, P | Placental thrombosis | Neg |
| 4 | F | 33 | H, Liv, **L**, **P** | Hydrops foetalis, cardiomegaly, hepatosplenomegaly, bilateral club feet, large placenta, nucleated red blood cells in placenta. | PVB 19 |
| 6 | M | 24 | H, Liv, L, P | Cause unknown | Neg |
| 9 | F | 23 | H, Liv, L, P | Acute chorioamnionitis | Neg |
| 10 | M | 29 | H, Liv, L | Low splenic weight, undescended testes | Neg |
| 11 | F | 33 | H, **Liv**, L, P | Hydrops foetalis, hepatomegaly | PVB 19 |
| 13 | F | 25 | **H**, Liv, L, P | Umbilical cord hemorrhage | PVB 19 |
| 14 | M | 37 | H, **Liv**, L | Hydrocephalus, 4 aortic arch, imperforate anus, absent of right umbilical artery, bilateral undescended testes, hypospadias, bilateral incomplete cleft palate, scoliosis, bilateral talipes equinovarus with bilateral pes planus | PVB 19 |
| 15 | F | 39 | **H**, Liv, L, P | Hydrocephalus, lung hypoplasia, Hydronephrosis with hydroureter both sides, subfalcine herniation shifted to left side | PVB 19 |
| 19 | F | 30 | H, Liv, L, P | Hydrops foetalis, hepatosplenomegaly, acute chorioamnionitis (Maternal syphilis) | Neg |
| 21 | M | 19 | H, Liv, L, P | Foetal anaemia due to premature separation of placenta | Neg |
| 25 | M | 19 | H, Liv, L, P | Hepatoblastoma | Neg |
| 27 | F | 21 | H, Liv, L, P | Acute chorioamnionitis | Neg |
| 28 | F | 36 | H, Liv, L, P | Foetal anaemia, unknown cause | Neg |
| 30 | F | 32 | **H**, Liv, L, P | Small placenta, placental insufficiency | PVB 19 |
| 32 | M | 37 | H, Liv, L, P | Small placental | Neg |
| 34 | M | 24 | H, Liv, L, P | Left lung one lobe, congenital pulmonary adenomatoid malformation | Neg |
| 36 | M | 32 | H, Liv, L, P | Acute chorioamnionitis (Maternal syphilis) | Neg |

***Note:***

- *Organs in bold are positive for viral DNA.*
- *F = Female; H = Heart; L = Lung; Li = Liver; M = Male; Neg = Negative; P = Placenta; PCR = Polymerase chain reaction; and PVB 19 = Parvovirus B19*

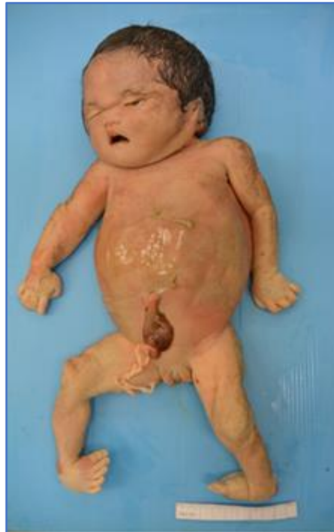

**Figure 1 Case number 4.** Moderately macerated female infant had positive for parvovirus B19 detection with hydropic features.

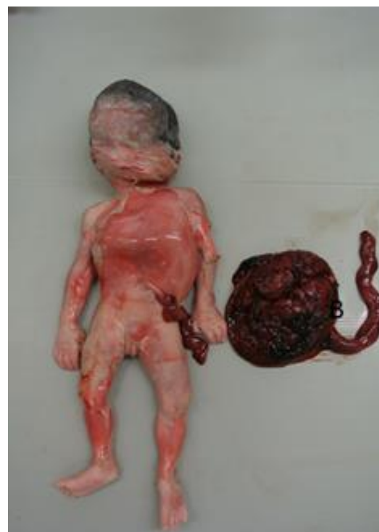

**Figure 2 Case number 30.** Moderately macerated female infant had positive for parvovirus B19 without hydropic features.

## Table 5 Autopsy findings in termination of pregnancy cases.

| Case number | Sex | Gestational age (Weeks) | Organ | Autopsy data | Viral PCR |
|---|---|---|---|---|---|
| 5 | M | 24 | H, Liv, L, P | Small placenta (Maternal HELLP syndrome) | Neg |
| 7 | M | 19 | H, **Liv**, L, P | Low set ear, umbilical hernia, undescended testes (Trisomy 18) | PVB 19 |
| 8 | M | 22 | H, Liv, **L**, P | Occipital meningoencephalocele, bilateral incomplete cleft palate, postaxial polydactyly, bilateral multicytic dyplastic kidney, pulmonary hyperplasia | PVB 19 |
| 12 | F | 18 | **H**, **Liv**, L, **P** | Ventricular septal defect, Omphalocele, club foot, spina bifida | PVB 19 |
| 16 | M | 21 | **H**, **Liv**, L, P | Short limb anomaly, short ribs with multiple fractures, femurs fractured | PVB 19 |
| 17 | No genitalia | 26 | H, Liv, L, P | Limb-body wall complex, Urogenital anomalies: No external genitalia, Left hydronephrosis and hydroureter, Kyphoscoliosis | Neg |
| 18 | F | 31 | H, Liv, L, P | Bilateral diaphragmatic hernia, hypertelorism, low set ear (trisomy 21) | Neg |
| 20 | F | 19 | H, Liv, L, P | Cystic hygroma, hydrops foetalis | Neg |
| 22 | F | 19 | H, Liv, L, P | Low-set both ears, rocker bottom | Neg |
| 23 | F | 18 | H, Liv, L, P | Distal arthrogryposis type I | Neg |
| 24 | F | 19 | H, Liv, L, P | Holoprosencephaly, bilateral cleft lip and complete cleft palate, absent brachiocephalic vein, bilateral superior vena cava, ventricular septal defect, overriding of aorta, pulmonary stenosis | Neg |
| 26 | F | 31 | H, Liv, L, P | Anencephaly, incomplete cleft palate | Neg |
| 29 | F, F | 21 | H, Liv, L, P | Thoraco-omphalopagus conjoined twins | Neg |
| 31 | F | 19 | H, Liv, L, P | Bart's hydrops foetalis | Neg |
| 33 | M | 20 | H, Liv, L, P | Renal hypoplasia, oligohydramnios, bilateral pulmonary hypoplasia | Neg |
| 35 | F | 21 | H, Liv, L, P | Single atria, ventricular septal defect, persistent left superior vena cava, pulmonary artery atresia, postaxial polydactyly of both hands and left foot | Neg |

***Note:***

- *Organs in bold are positive for viral DNA.*
- *F = Female; H = Heart; L = Lung; Li = Liver; M = Male; Neg = Negative; P = Placenta; PCR = Polymerase chain reaction; and PVB 19 = Parvovirus B19*

## Conclusion

At Srinagarind Hospital, the prevalence of parvovirus B19 DNA detection rate in foetal death *in utero* is higher than previously studied.

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## CASE REPORT

# Metastatic prostatic adenocarcinoma mimicking plasmablastic lymphoma: diagnostic pitfalls

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## Abstract

Plasmablastic lymphoma was diagnosed in a lymph node biopsy based on morphology and immunophenotypic findings of positivity with CD138, MUM1 and EMA, and negativity with CD3, CD10, CD20, CD30, CD56, chromogranin, synaptophysin, CK7 and CK20. Upon the review, the neoplastic cells have distinct central nucleolus and modest to large amount of cytoplasm but somewhat cohesive with some nuclear molding and some clear cytoplasm. All the immunophenotypic findings were interpreted similarly except for cytoplasmic MUM1 positivity and focal CD10 positivity. Histochemical staining showed lack of mucin or glycogen. Additional immunostaining showed negative CD38, kappa and lambda light chains, but positive AE1/AE3, CK19, PSA and NKX3.1. Thus, upon the review, plasmablastic lymphoma was excluded and metastatic prostatic adenocarcinoma was given. Prostatic biopsy confirmed prostatic adenocarcinoma with morphology similar to that shown in the lymph node biopsy. In summary, diagnostic pitfalls occurred due to cross reactivity with CD138 in carcinoma cells as well as focal CD10 positivity and cytoplasmic positivity of MUM1 but double negative cytokeratins ($CK7^-$ and $CK20^-$) in carcinoma cells. To prevent misdiagnosis in this scenario, AE1/AE3 is a must for carcinoma screening and making the diagnosis of plasmablastic lymphoma should follow strictly the typical morphologic and immunophenotypic findings.

**Keywords:** CD138; cross reactivity; diagnostic pitfall; metastatic prostatic adenocarcinoma; plasmablastic lymphoma

## Introduction

In general, metastatic prostatic adenocarcinoma does not create diagnostic difficulty when the clinical information of prostatic adenocarcinoma is established and morphology of metastatic carcinoma to the regional lymph node shows typical glandular formation for adenocarcinoma. Nevertheless, prostatic cancer can produce an enlarged lymph node or generalised lymphadenopathy mimicking malignant lymphoma[1-3]. Moreover, it may have histologic features that look like lymphoma[4]. We herein report an interesting case of metastatic prostatic adenocarcinoma mimicking plasmablastic lymphoma due to diagnostic pitfalls including cross reactivity with CD138 in carcinoma cells, focal CD10 positivity, cytoplasmic positivity of MUM1 and double negative cytokeratins (CK7- CK20-) in carcinoma cells.

## Case Report

A 64-year-old man presented at a provincial hospital with left lower quadrant abdominal pain. Investigation showed para-aortic lymphadenopathies and a presacral soft tissue mass with bone lesion. Exploratory laparotomy and biopsy of the enlarged lymph node were performed. The tissue sample was submitted to a private pathology laboratory. The pathology report described 3 pieces of rubbery oval shaped tan white lymph nodes, varying from 1.0 x 0.7 x 0.5 cm to 1.8 x 1.2 x 0.5 cm in size. The cut surface of each piece was homogeneously rubbery tan white. All pieces were embedded for histologic evaluation.

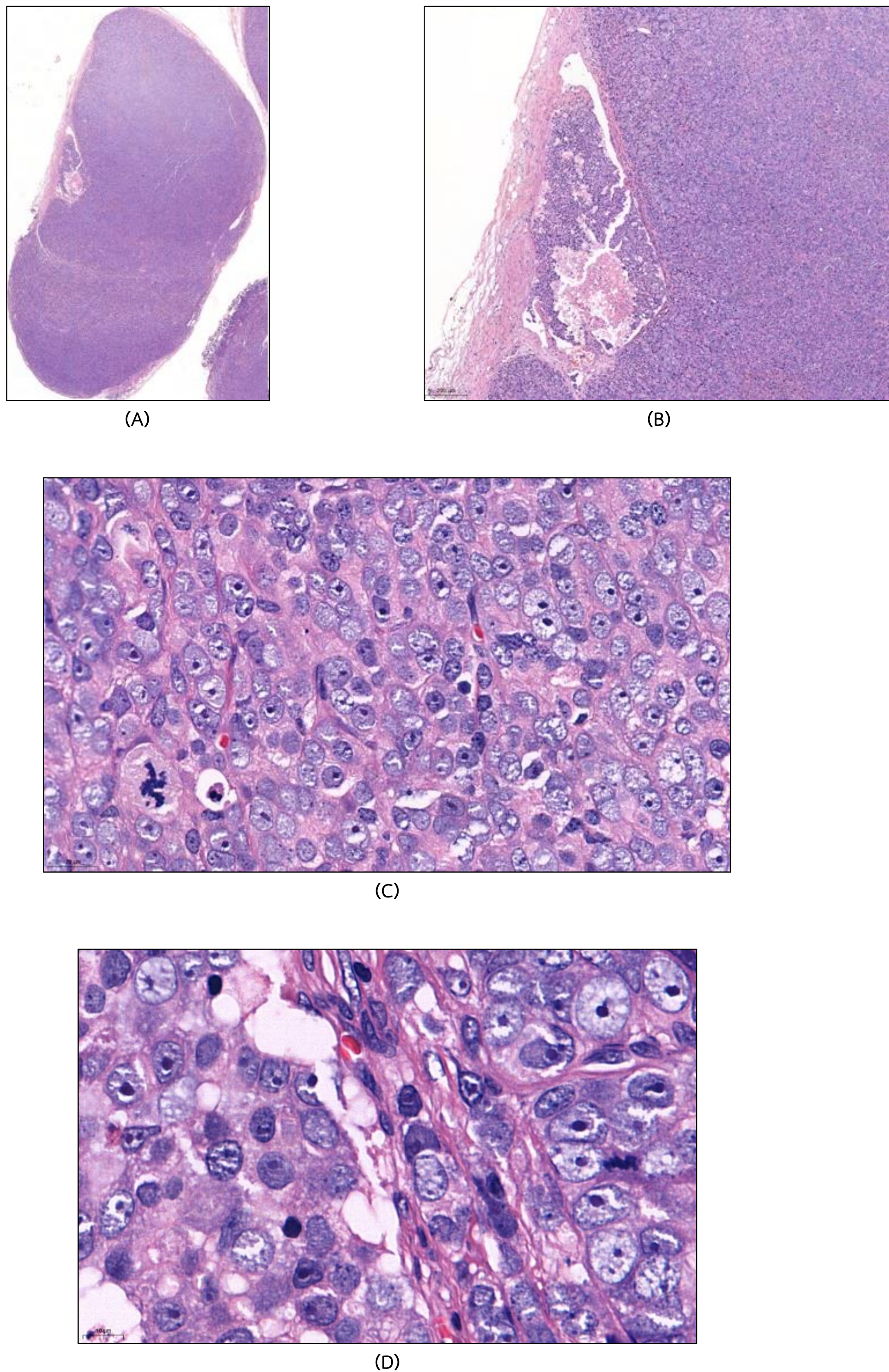
The first pathologist described effacement of lymphoid structure by diffuse large neoplastic lymphoid cells, reported as "compatible with diffuse large B-cell lymphoma (DLBCL)" (*Figure 1*) and suggested immunohistochemical staining (immunostaining) for CD3, CD20 and CD45. But immunostaining was performed for CD45, CD20, CD10, BCL2, BCL6, MYC and MUM1. The results were all reported as negative except for weakly positive BCL6 and positive MYC with moderate intensity. The first pathologist queried plasmablastic lymphoma or metastatic carcinoma so that additional immunostaining was performed for CD138, CD79a, CK7, CK20, CD56, synaptophysin, chromogranin, S-100, melan A, HMB45, EMA, CD3, CD30, ALK1 and in situ hybridisation for EBV-encoded small RNA (EBER). The results were reported as positive CD138 (nearly 100%, moderate intensity), EMA (approximately 50%) and synaptophysin (few, focal, and weak) while the others were all negative. The first pathologist finally gave the final diagnosis as primary extramedullary plasmacytoma of the lymph node

and recommended further immunostaining for kappa and lambda light chains after a month-long period of performing a large panel of immunostaining for 22 tests, including EBER ISH.

Haematologic evaluation was then performed. The patient had anaemia without any other myeloma defining events. Bone marrow examination showed slight increase in plasma cells (6 – 8% of total nucleated marrow cells) but the patient does not have monoclonal gammopathy. Later, the patient had complaint of difficult micturition. Physical examination revealed prostatic enlargement and laboratory finding showed elevated serum PSA. Prostatic biopsy confirmed that the patient had prostatic adenocarcinoma with Gleason score = 8 (5 + 3). So, the attending haematologist (YJ) doubted about the diagnosis of the lymph node biopsy. She decided to submit all the slides and tissue blocks of the lymph node biopsy to Siriraj Hospital for haematopathology consultation (SS).

Morphological review showed the neoplastic cells with distinct central nucleolus and modest to large amount of cytoplasm but somewhat cohesive with occasional nuclear molding and clear cytoplasm. The review of the immunostaining and EBER ISH results were positive CD138, faint positive BCL6, focal positive CD10 with cytoplasmic staining (20%), some positive MYC protein, some positive EMA with cytoplasmic staining, some positive MUM1 with cytoplasmic staining (but no nuclear staining) and some positive synaptophysin with cytoplasmic staining (2 – 3%) (*Figure 2*), while the others, including EBER ISH, were negative.

Additional histochemical stains performed at Siriraj Hospital showed that the tumour cells were negative for mucin, glycogen and basophilia. Small nests of tumour cells were surrounded by reticulin fibres. At this point, metastatic carcinoma was the preferred diagnosis. Based on $CK7^{-}/CK20^{-}$ pattern and focal CD10 expression, the possible primary sites included prostate, pancreas and liver. A number of immunostaining was eventually performed for AE1/AE3, SOX-10, CD38, kappa, lambda, PSA, NKX3.1, CK19, PAX8, glypican-3 and AFP (total of 11 tests). The results showed positive CK19, PSA, NKX3.1 and focal positive AE1/AE3 in the tumour cells (*Figure 3*), while the others were negative. Thus, finally, the lymph node in fact showed metastatic prostatic adenocarcinoma.



(A) (B)

(C)

(D)

**Figure 1 Histology of the excised para-aortic lymph node. (A)** Low magnification of the involved lymph node showing diffuse effacement of lymph node architecture that may resemble lymphomatous involvement. **(B)** Subcapsular lymph node sinus filled by tumour cells with some cohesiveness. **(C)** Diffuse proliferation with large tumour cells with some cohesiveness. Nests of tumour cells are vaguely appreciated as well as some nuclear molding. **(D)** Large tumour cells with distinct centrally located nucleolus and appreciable amount of cytoplasm resembling plasmablasts.

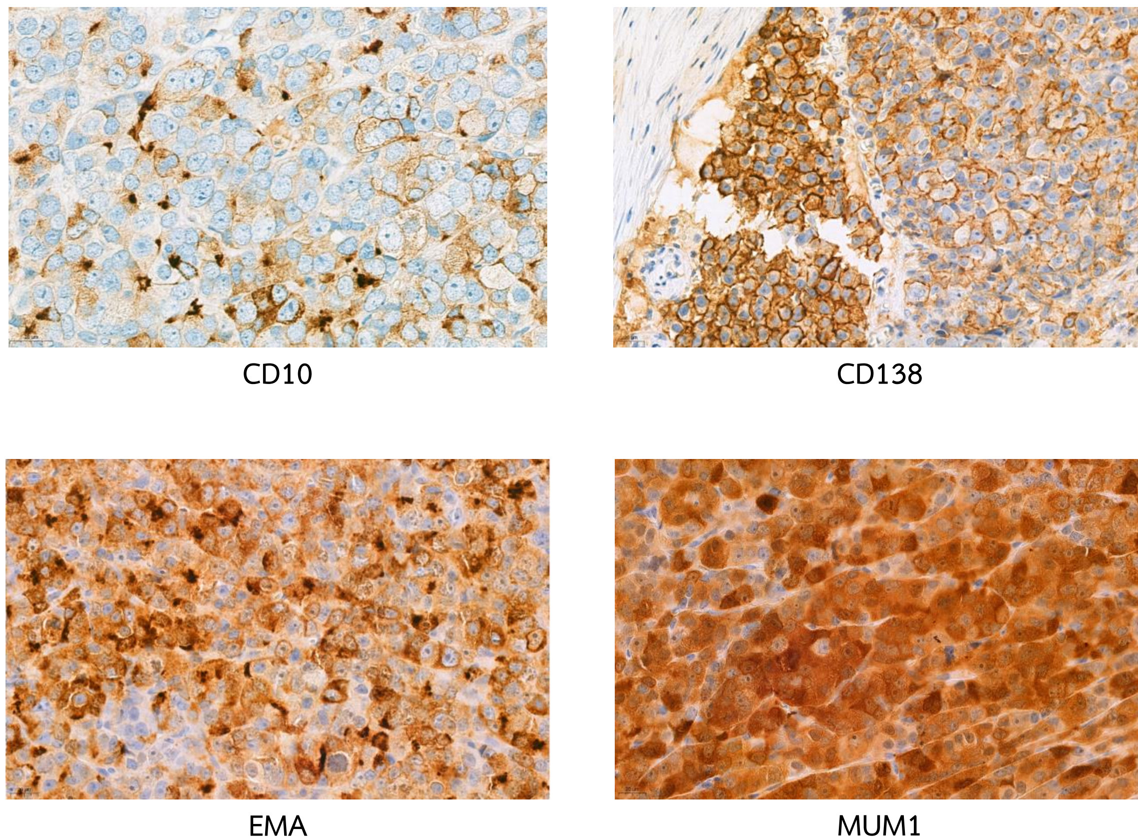



**Figure 2 High magnification of positive CD10, CD138, EMA and MUM1 immunohistochemical stainings of the excised para-aortic lymph node.**

## Discussion

Plasmablastic lymphoma is an uncommon entity of non-Hodgkin lymphoma. After the first report of 16 cases involving oral cavity with underlying HIV infection(5), It has been introduced since 2001 in the WHO classification under the other rare variants/subtypes of diffuse large B-cell lymphoma (DLBCL) with distinctive immunophenotypic features(6). By morphology, it is indistinguishable from immunoblastic variant of DLBCL that requires majority of the lymphoma cells (> 90%) with immunoblasts showing a single centrally located nucleolus and an appreciable amount of basophilic cytoplasm. By immunophenotype, few if any of the lymphoma cells in plasmablastic lymphoma are positive for CD20 and CD45 but the lymphoma cells do express plasma cell markers such as Vs38c and CD138.

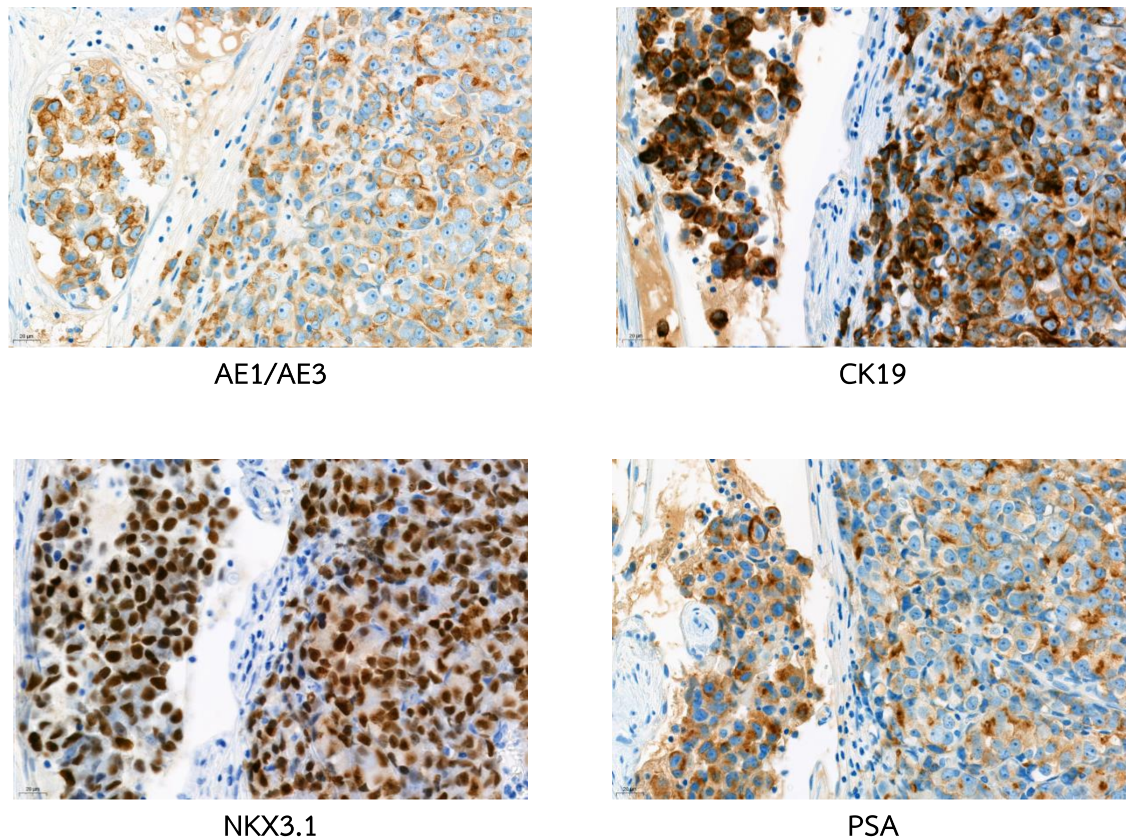



**Figure 3 High magnification of positive AE1/AE3, CK19, NKX3.1 and PSA immunohistochemical stainings of the excised para-aortic lymph node.**

Originally in WHO classification 2001, plasmablastic lymphoma is characterised by high growth fraction (proliferation index), absence of mature monoclonal plasma cells, and salient clinical feature (oral cavity lesion in the setting of HIV infection) that help to distinguish plasmablastic lymphoma from plasma cell myeloma. Approximately 60% of cases contain EBV. Then, in WHO classification 2008, plasmablastic lymphoma has been accepted as a genuine entity defined as a diffuse proliferation of large lymphoma cells mostly resembling B immunoblasts but with immunophenotype of plasma cells. It predominantly involves extranodal sites not only in oral cavity[7]. Morphology expands to a spectrum varying from a diffuse and cohesive proliferation of cells resembling immunoblasts (commonly seen in the originally described oral cavity lesions in the setting of HIV infection) to cells with more obvious plasmacytic differentiation that may resemble plasmablastic variant of plasma cell myeloma (commonly seen in the other extranodal sites and lymph node). Immunophenotypic findings include positive plasma cell markers (CD138, CD38, Vs38c, and IRF4/MUM1) and negative or

only weakly positive B-cell markers (CD20, PAX5) or CD45 except for CD79a that can be positive in 50 – 85% of cases. Light chain restriction, either of kappa or lambda, can be found in 50 – 70% of cases and predominantly with IgG. CD56 is usually negative in the oral cavity lesion but it may be seen in cases at other sites with plasmacytic differentiation. Cases with CD56 expression, however, should include underlying plasmablastic variant of plasma cell myeloma in differential diagnosis. Expression of EMA and CD30 is frequent. EBER ISH is positive in 60 – 75% of cases, but nearly 100% in the oral cavity lesion in association with HIV infection.

In the most recent WHO classification 2017, plasmablastic lymphoma remains mostly the same but it includes not only cases with HIV infection but also cases in association with other causes of immunodeficiency. However, cases of large B-cell lymphoma with a plasmablastic immunophenotype such as ALK-positive large B-cell lymphoma and HHV-8-associated lymphoproliferative disorders are not included in plasmablastic lymphoma[8]. Nodal involvement is found in less than 10% of cases overall, but in 30% of post-transplant cases. Cases with prior plasma cell myeloma should be considered plasmablastic transformation of myeloma and distinguished from primary plasmablastic lymphoma. In addition to WHO classification 2008, the lymphoma cells are positive for PRDM1 (BLIMP1) and XBP1. The Ki-67 proliferation index is usually very high (> 90%). The expression of BCL2 and BCL6 is usually absent. CD10 can be positive in 20% of cases. But strong expression of CD20, CD79a, and PAX5 should not be considered plasmablastic lymphoma.

In the present case, plasmablastic lymphoma is considered in the differential diagnosis by morphology and positivity with CD138. But, after showing the lack of EBER positivity in the tumour cells, it was given as a final diagnosis by the first pathologist as primary extramedullary plasmacytoma of the lymph node instead. A number of diagnostic pitfalls in this particular lymph node biopsy included: 1) impression of malignant lymphoma as the first pathologist gave at the preliminary report; 2) awareness of positive CD138 in non-haematologic malignancy; 3) order immunostaining for CK7 and CK20 but missing AE1/AE3; and 4) misinterpretation of some subtle findings such as focal positive CD10 with cytoplasmic staining (20%), some positive EMA with cytoplasmic staining, and some positive MUM1 with cytoplasmic staining (but no nuclear staining). Despite the lack of common markers for lymphoma (CD3, CD20, CD30 and CD45), the first pathologist still believed in plasmablastic lymphoma. However, he/she gave the final diagnosis of extramedullary plasmacytoma after the tumour cells showed CD138 positivity but lacking EBER positivity. Diagnostic pitfalls then rely on the awareness of positive CD138 in non-haematologic malignancy that is well

documented. The first pathologist was presumably aware of this as immunostaining for kappa and lambda was recommended in the pathology report.

Besides plasma cells and plasmacytic neoplasms, including plasmacytoma, plasma cell myeloma and plasmablastic lymphoma, CD138 has been reported in a number of non-haematologic malignancy such as adenocarcinoma [lung (83%), colorectum (85%), pancreas (73%), stomach (54%) or prostate (16%)], squamous cell carcinoma [oesophagus (100%), vagina (90%), lung (86%), uterine cervix (80%) or vulva (73%)] and invasive urothelial carcinoma (76%)[9]. In order to avoid misinterpretation of CD138 as the only marker of plasma cell phenotype in undifferentiated neoplasm, one should evaluate at least for AE1/AE3. CD38 is more reliable for plasmacytic neoplasms. However, it can be expressed by haematopoietic stem cells so that some leukemic cells may express CD38[10] and some aggressive non-Hodgkin lymphoma can express CD38 (such as primary effusion lymphoma)[11].

Evaluation of CK7 and CK20 without AE1/AE3 is another diagnostic pitfall in this particular case. It is well documented that $CK7^{-}/CK20^{-}$ pattern can be seen in prostatic adenocarcinoma, clear cell renal cell carcinoma, hepatocellular carcinoma, adrenocortical carcinoma, non-seminoma germ cell tumour, mesothelioma, small cell lung carcinoma and gastric adenocarcinoma[12]. In this particular case, if the first pathologist approached with the conventional 4 markers for first panel of immunostaining in undifferentiated neoplasm, including AE1/AE3, CD45, S-100 and vimentin, the number of tests in immunostaining would have been limited to 4 markers as metastatic undifferentiated carcinoma should be reached. Then, it depends on the clinical information as in this particular case, metastatic prostatic adenocarcinoma can be diagnosed by the $CK7^{-}/CK20^{-}$ pattern and positive PSA and/or NKX3.1 so that such a definite diagnosis could be given by markers for immunostaining not more than 10.

Some subtle findings that were misinterpreted in these particular cases such as focal positive CD10 with cytoplasmic staining (20%), some positive EMA with cytoplasmic staining and some positive MUM1 with cytoplasmic staining (but no nuclear staining) could be overlooked. But if one recognises these subtle findings, further search in the literature could lead to the possibility of carcinoma in this particular case. Diffuse cytoplasmic staining with CD10 could be seen in prostatic adenocarcinoma[13]. EMA positivity in prostatic adenocarcinoma is mainly on the luminal membranes of malignant acini, with some cytoplasmic staining particularly in poorly-differentiated carcinoma[14]. MUM1 positivity is quite specific in haematologic malignancy and it needs to be nuclear staining with some weak to

moderate cytoplasmic staining in most cases. However, MUM1 positivity could be found in a subset of malignant melanoma but not in other non-haematologic malignancy[15]. This present case may be the first case of poorly-differentiated prostatic adenocarcinoma to have only cytoplasmic staining with MUM1 but no nuclear staining.

Even this patient did not have problem of difficult micturition that led to urological work-up and the diagnosis of prostatic adenocarcinoma, the attending haematologist still wanted to review this particular lymph node biopsy after excluding plasma cell myeloma. Primary extramedullary plasmacytoma of the lymph node given by the first pathologist was rare and it could not explain para-aortic lymphadenopathies and a presacral soft tissue mass with bone lesion. Moreover, plasmacytoma usually has morphologic features of mature plasma cells, not plasmablast like morphology[11]. Plasmablastic lymphoma mentioned in the report during work-up by the first pathologist might be more accepted. Certainly, an appropriate panel of immunostaining should reveal that, in fact, this is a case of metastatic prostatic adenocarcinoma as shown above.

## Conclusion

Diagnostic pitfalls in the present case of metastatic prostatic adenocarcinoma occurred due to cross reactivity with CD138 in carcinoma cells as well as focal CD10 positivity and cytoplasmic positivity of MUM1 but double negative cytokeratins ($CK7^-$ and $CK20^-$) in carcinoma cells. To prevent misdiagnosis in this scenario, AE1/AE3 is a must for carcinoma screening and making the diagnosis of plasmablastic lymphoma should follow strictly the typical morphologic and immunophenotypic findings.

## Acknowledgement

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# APPENDIX 1
# INFORMATION FOR AUTHORS

All authors listed in a paper submitted to Asian Archives of Pathology (AAP) must have contributed substantially to the work. It is the corresponding author who takes responsibility for obtaining permission from all co-authors for the submission. When submitting the paper, the corresponding author is encouraged to indicate the specific contributions of all authors (the author statement, with signatures from all authors and percentage of each contribution can be accepted). Examples of contributions include: designed research, performed research, contributed vital new reagents or analytical tools, analysed data, and wrote the paper. An author may list more than one type of contribution, and more than one author may have contributed to the same aspect of the work.

Authors should take care to exclude overlap and duplication in papers dealing with related materials. See also paragraph on Redundant or Duplicate Publication in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" at http://www.icmje.org/index.html.

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AAP uses **DOUBLE-BLIND PEER REVIEW** for all articles it publishes. **Each submitted manuscript is reviewed by THREE members of the Editorial Board or THREE scholars from different institutions**. **A procedure keeps both the author and the reviewers anonymous**, hence the term '*double-blind*'. The decision (reject, invite revision and accept) letter will be coming from the Editorial Board after completing the manuscript's review. The editor's decision is based not just on technical merit of the work, but also on other factors such as the priority for publication and the relevance to the Journal's general readership. All papers are judged in relation to other submissions currently under consideration.

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The letters to the editor are the reactions to any papers published in AAP. These letters will be reviewed by the Editorial Board and sent to the authors of the original paper with an invitation to respond. Letters and eventual responses will be published together, when appropriate.

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- *Figure or Table: Maximum of 1 (if needed)*

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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.

- *Word Count: 3,000 – 5,000 words (excluding abstract, references, and figure or table legends)*
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- *References: Maximum of 150*
- *Figures or Tables: Maximum of 6*

3. **Review Articles**

The review articles are generally invited by the Editor-in-Chief. They should focus on a topic of broad scientific interest and on recent advances. These articles are peer-reviewed before the final decision to accept or reject the manuscript for publication. Therefore, revisions may be required.

- *Word Count: 3,000 – 5,000 words (excluding abstract, references, and figure or table legends)*
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## 4. Case Reports

AAP limits publication of case reports to those that are truly novel, unexpected or unusual, provide new information about anatomical pathology, clinical pathology (laboratory medicine) or forensic medicine (legal medicine or medical jurisprudence). In addition, they must have educational value for the aforementioned fields. The journal will not consider case reports describing preventive or therapeutic interventions, as these generally require stronger evidence. Case reports that involve a substantial literature review should be submitted as a review article. The submitted case reports will undergo the usual peer-reviewed process.

- *Word Count: 1,200 – 2,000 words (excluding abstract, references, and figure or table legends)*
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- *References: Maximum of 20*
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Case illustrations are aimed to provide education to readers through multidisciplinary clinicopathological discussions of interesting cases. The manuscript consists of a clinical presentation or description, laboratory investigations, discussion, final diagnosis, and up to 5 take-home messages (learning points). Regarding continuous learning through self-assessment, each of the case illustrations will contain 3 – 5 multiple choice questions (MCQs) with 4 – 5 suggested answers for each question. These MCQs are placed after the final diagnosis and the correct answers should be revealed after the references. The questions and take-home messages (learning points) are included in the total word count. The manuscripts that have passed an initial screening by the Editorial Board will be reviewed by two experts in the field.

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- *<u>Abstract</u>: Not required*
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- *<u>Figures</u>: Maximum of 2*
- *<u>Tables</u>: Maximum of 5*

### 6. Technical Notes

The technical notes are brief descriptions of scientific techniques used in the anatomical pathology, clinical pathology (laboratory medicine), forensic medicine (legal medicine or medical jurisprudence), molecular medicine or pathobiology. The submitted manuscripts are usually peer-reviewed.

- *<u>Word Count</u>: Maximum of 1,000 words (excluding references and figure or table legends)*
- *<u>Abstract</u>: Not required*
- *<u>References</u>: Maximum of 5*
- *<u>Figures or Tables</u>: Maximum of 2*

## Organisation of Manuscripts

### 1. General Format

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 be typed in 12-point regular Times New Roman font for English manuscript and 16-point regular TH SarabunPSK font for Thai manuscript.

The running titles of English and Thai manuscripts are placed in the top left-hand corner of each page. They cannot exceed 50 characters, including spaces between words and punctuation. For the header of English paper, the running title will be typed in all capital letters. The page number goes on the top right-hand corner.

Footnotes are not used in the manuscripts, but parenthetical statements within text are applied instead and sparingly. Abbreviations should be defined at first mention and

thereafter used consistently throughout the article. The standard abbreviations for units of measure must be used in conjunction with numbers.

All studies that involve human subjects should not mention subjects' identifying information (e.g. initials) unless the information is essential for scientific purposes and the patients (or parents or guardians) give written informed consent for publication.

## 2. Title Page

The title page is the first page of the manuscripts and must contain the following:

- The title of the paper (not more than 150 characters, including spaces between words)
- The full names, institutional addresses, and email addresses for all authors (If authors regard it as essential to indicate that two or more co-authors are equal in status, they may be identified by an asterisk symbol with the caption "These authors contributed equally to this work" immediately under the address list.)
- The name, surname, full postal address, telephone number, facsimile number, and email address of the corresponding author who will take primary responsibility for communication with AAP.
- Conflict of interest statement (If there are no conflicts of interest for any author, the following statement should be inserted: "The authors declare that they have no conflicts of interest with the contents of this article.")

## 3. Abstract

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

- *Background: The main context of the study*
- *Objective: The main purpose of the study*
- *Materials and Methods: How the study was performed*
- *Results: The main findings*
- *Conclusions: Brief summary and potential implications*
- *Keywords: 3 – 5 words or phrases (listed in alphabetical order) representing the main content of the article*

## 4. Introduction

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.

## 5. Materials and Methods

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.

All studies involving animal or human subjects must abide by the rules of the appropriate Internal Review Board and the tenets of the recently revised Helsinki protocol. Hence, the manuscripts must include the name of the ethics committee that approved the study and the committee's reference number if appropriate.

## 6. Results

The Results section should concisely describe the findings of the study including, if appropriate, results of statistical analysis which must be presented either in the text or as tables and figures. It should follow a logical sequence. However, the description of results should not simply repeat the data that appear in tables and figures and, likewise, the same data should not be displayed in both tables and figures. Any chemical equations, structural formulas or mathematical equations should be placed between successive lines of text. The authors do not discuss the results or draw any conclusions in this section.

## 7. Discussion

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.

## 8. Conclusion

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.

## 9. Acknowledgements

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

- *Funding sources*
- *A person who provided purely technical help or writing assistance*
- *A department chair who provided only general support*
- *Sources of material (e.g. novel drugs) not available commercially*

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- *Journal article*

    1. Sibai BM. Magnesium sulfate is the ideal anticonvulsant in preeclampsia – eclampsia. Am J Obstet Gynecol 1990; 162: 1141 – 5.

- *Books*
  2. Remington JS, Swartz MN. Current Topics in Infectious Diseases, Vol 21. Boston: Blackwell Science Publication, 2001.
- *Chapter in a book*
  3. Cunningham FG, Hauth JC, Leveno KJ, Gilstrap L III, Bloom SL, Wenstrom KD. Hypertensive disorders in pregnancy. In: Cunningham FG, Hauth JC, Leveno KJ, Gilstrap L III, Brom SL, Wenstrom KD, eds. Williams Obstetrics, 22$^{nd}$ ed. New York: McGraw-Hill, 2005: 761 – 808.

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- *References*
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- *Figure (if needed)*

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- *Structured Abstract*
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- *Materials and Methods*
- *Results*
- *Discussion*
- *Conclusions*
- *Acknowledgements*
- *References*
- *Table (s)*

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

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- *Unstructured Abstract*
- *Introduction*
- *Main Text*
- *Conclusions*
- *Acknowledgements*
- *References*
- *Table (s)*
- *Figure Legend (s)*
- *Figure (s)*

**14.4. Case Reports**

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- *Case Description*
- *Discussion*
- *Conclusions*
- *Acknowledgements*
- *References*
- *Table (s)*
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- *Figure (s)*

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- *Laboratory Investigations*

- *Discussion*
- *Final Diagnosis*
- *Multiple Choice Questions (MCQs)*
- *Take-Home Messages (Learning Points)*
- *Acknowledgements*
- *References*
- *Correct Answers to MCQs*
- *Table (s)*
- *Figure Legend (s)*
- *Figure (s)*

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- *Table (s)*
- *Figure Legend (s)*
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Announcements of academic meetings and conferences that are of interest to the readers of Asian Archives of Pathology (AAP) should be sent to the Editor-in-Chief at least 3 months before the first day of the month of issue. The contact information is shown below.

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