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AD Express

June 2023

Editorial board

From the Editors' Desk

Dear Reader,

The future portents well for laboratory medicine. The advent of evidence based medicine, the ever-growing advances in laboratory medicine & the ongoing COVID pandemic, have crystallized the importance of laboratory professionals in healthcare. Lab Professional's Week is celebrated worldwide in the last week of April & 'Team Apollo Diagnostics' recapitulated this year's theme "The future is lab" in a week filled with lively activity which reflected the talent & expertise that the AD fold possesses in a one of a kind event that will be remembered for long!

In this sixth edition of the year, we share an interesting repertoire of topics. Our case reports are an esoteric mix of a rare fetal autopsy to a diagnostic dilemma in a common soft tissue tumour can pose significant diagnostic challenge & we share findings from acommon 'histopathology' entity from the soft tissue realm that presented with interesting findings.

Astute judgment & robust background of the role played by the acute phase reactants, factors that take part in acute inflammation underlines the approach to be taken while investigating inflammatory disorders. The first article sheds light on CRP, a trustworthy marker on which clinical teams heavily depend upon. In the recent years, advances in molecular biology & cytogenetics have ushered in specific targeted therapy for tumours that had a grave prognosis yester while. The second article touches upon & advocates the importance of investigating for specific mutations in tumours of the central nervous system.

We expect our creative tendencies to gravitate towards biochemistry ballads, serology sonnets & musings from microbiology in the forthcoming issues. In a first attempt we share a Sonnet& quiz on 'white blood cells.' We have introduced another dimension to our quizzes by introducing 'know your crystal.' A strong background of morphology will augur good for any laboratory & a quiz on the above lines will help technologists appreciate morphology better.

We thank the contributors for taking time to put pen to paper & covering a gamut of topics with aplomb. AD express has gained considerable impetus by the way of your contributions & we welcome more from you all.Also humbly request you to share your feedback on 'AD express' & we assure you that feedback from you will make each next issue even more interesting !

Wishing you all a happy reading & a great year ahead!

Best regards,

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Contents

CASE REPORT

1. A Novel Association of Bilateral Multicystic Renal Dysplasia with Hirschsprung Disease

Dr. Marquess Raj - ZTC - Tamilnadu and Pondicherry &
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Background:

Meckel Gruber Syndrome (MKS) is a rare autosomal recessive malformation syndrome with a neural tube defect leading to death of the fetus in utero or shortly after birth. First reports of MKS were published in 1822 by Johann Friedrich Meckel (1). G.B.Gruber also published reports of patients with MKS in 1934 and gave it the name dysencephalia splanchnocystica (2). MKS is characterized by triad of large polycystic kidneys (100%), occipital encephalocele (90%), and postaxial polydactyly (83.3%) (3). Associated abnormalities include oral clefting, genital anomalies, CNS malformations and liver fibrosis. Mortality rate is 100% with most fetuses surviving only few days to weeks. Pulmonary hypoplasia is the leading cause of death. Worldwide incidence is 1/13,250-140,000 live births. There is a predilection for Belgian 1/3000) and Finnish (1/9000) populations (4). In India, highest incidence is in Gujarati Indians (1 affected birth per 1,300) (5).The aim of this study was to examine the products of conception & confirm the diagnosis of MKS.

Case presentation:

A 25 year old lady presented with missed abortion at 17 weeks of gestation on her first conception.There was no history of previous fetal demise or any congenital anomaly. History of consanguineous marriage was not present.Planned termination of pregnancy was performed & the products of conception were sent for study to the laboratory for autopsy, Histopathological examination & genetic studies. Informed consent was taken from the physician as well as the patient for genetic testing.

Discussion:

Ultrasonography had revealed no fetal heart activity indicating fetal death in utero. Other positive findings were occipital encephalocele measuring - 12 X 3 Cm. Both kidneys were enlarged hyperechoic &Multicystic.Right kidney measured 5.5 x 2.5 Cm. Left kidney measured 5.3 x 2.3 Cm. Rest of the organs did not reveal any gross abnormality. No further tests like karyotyping or AFP (alpha fetoprotein) were performed.The ultra-sonogram image was not retrievable from the patient & further study was performed on the products of conception which was received in saline.

Fetal skin taken from the cubital fossa was sent for karyotyping. A partial fetal autopsy was also performed in accordance with the statutory compliances of India & the state where the autopsy was performed (6).

Partial fetal autopsy was done with the intention of preserving the rare specimen for future academic study. Partial autopsy did not involve opening of the cranium considering the fragile nature of the encephalocele.

The ultra-sonogram findings correlated with the gross findings of the conceptus. The stage of fetal development correlated with 17 weeks of gestation.There was an encephalocele measuring 12 x 3 cm in the occipital region of the abortus **(Fig 1.)**.There were six digits both the lower limb extremities & right upper limb confirming polydactyly **(Fig 2)** & male genitalia was noted **(Fig 3)**. All the abdominal,thoracic & pelvic organs corresponded to 17 weeks of gestation. Both the kidneys were fused in the midline. The only gross abnormality noted was that the kidneys showed multiple cysts **(Fig 4.)** ranging from 0.1 to 0.3 mm in diameter, confirming the ultra-sonogram findings.

No other gross abnormalities were found in the other abdominal & thoracic organs either on gross or on cut section.

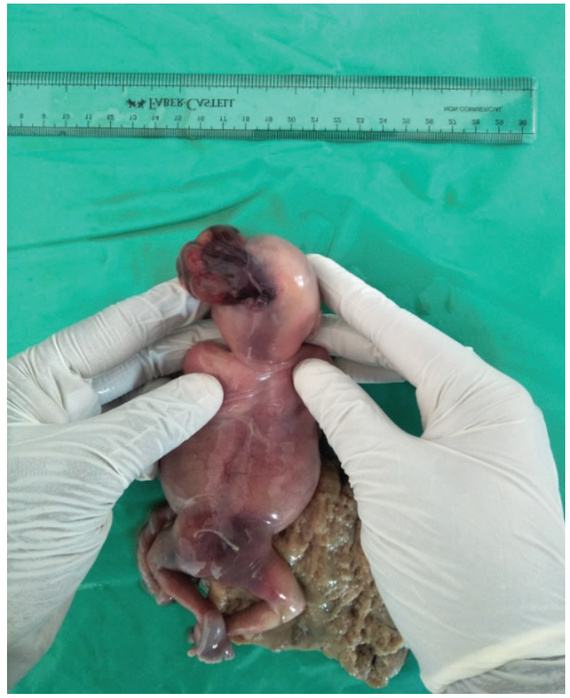

Fig 1. Showing occipital encephalocele

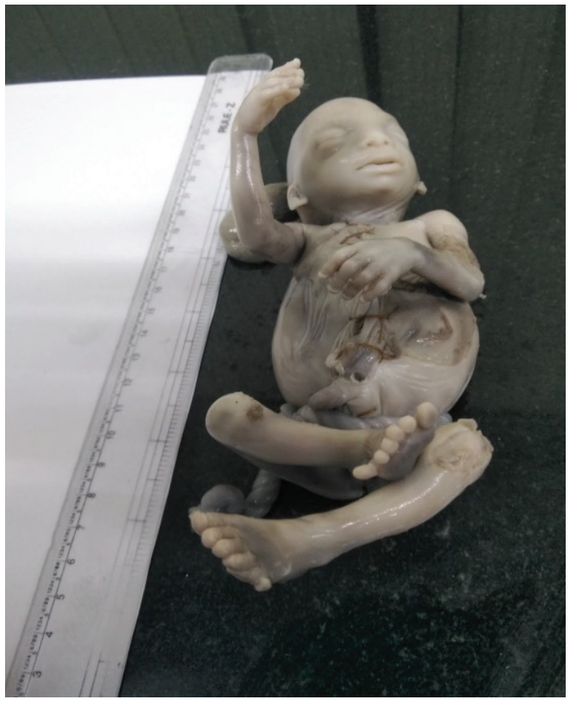

Fig 2. Polydactyly in the right upper & lower limb

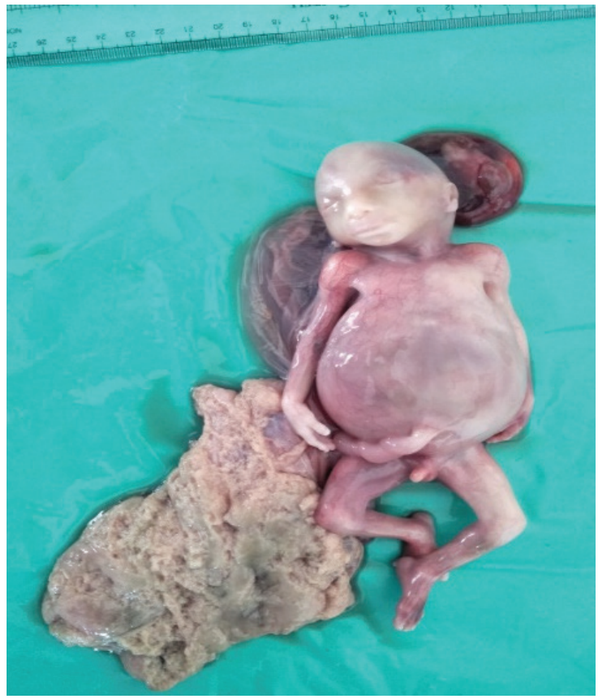

Fig 3. Showing male genitalia

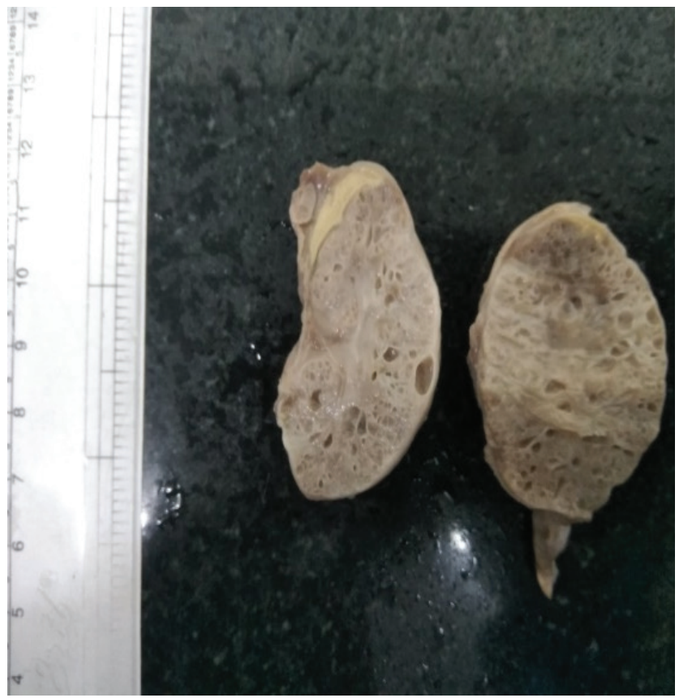

Fig 4. Tiny cysts on cut section of kidney

Histopathological examination was done on sections taken from both the kidneys & liver. Sections studied from both the kidneys showed fetal glomeruli & cystic dilation of the tubules corresponding with the micro-cysts on gross morphology **(Fig 5).** The sections studied from the liver showed evidence of fetal hematopoiesis **(Fig 6).**

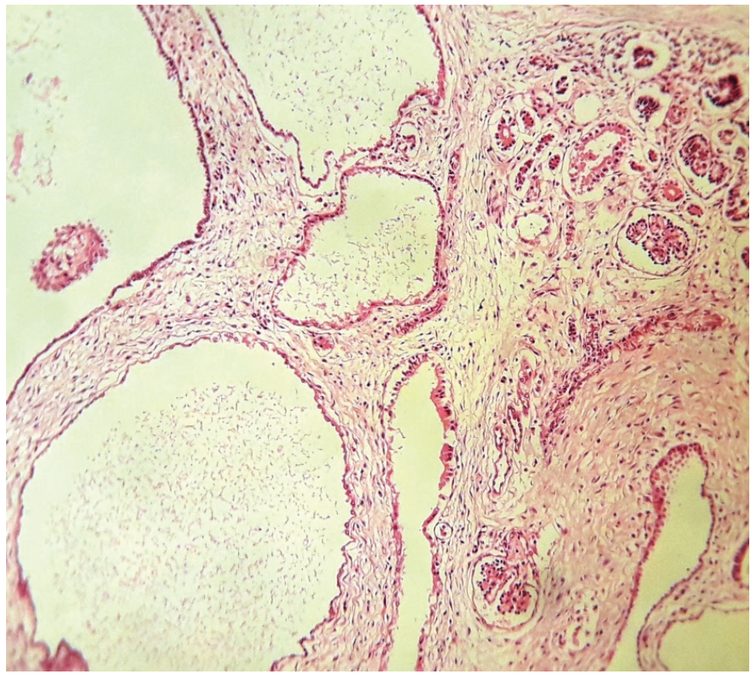

Fig 5.
Photomicrograph from section taken from the right kidney shows fetal glomeruli & multiple cystically dilated tubules (4 X).Sections studied from the left kidney also showed similar features.

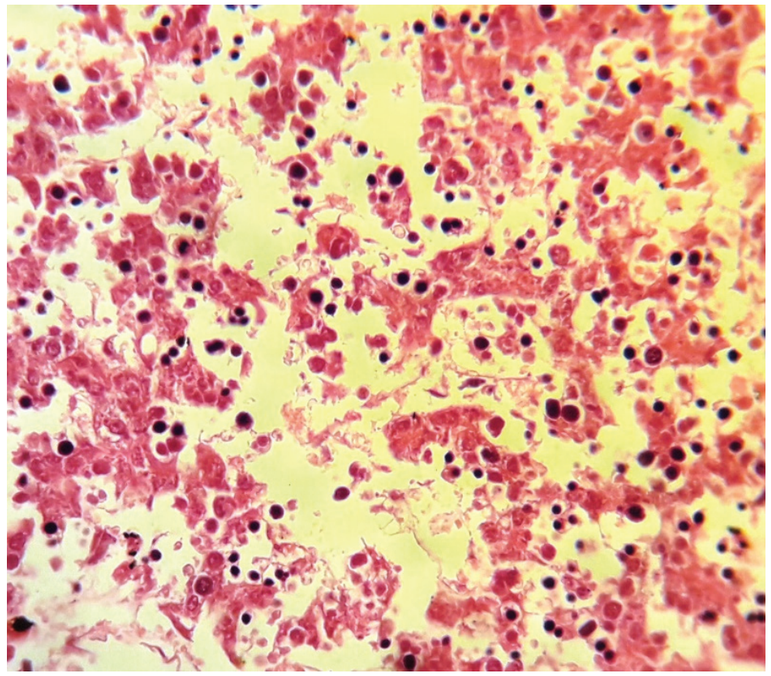

Fig 6.
Photomicrograph from section taken from the liver shows evidence of fetal haematopoiesis (4X).

Cytogenetic evaluation on the products of conception specimen revealed contamination at source in both short term & long term tissue cultures. However fluorescence is-situ hybridization on cells from direct culture reveals normal genetic constitution for the chromosomes 13,18,21 & sex chromosomes in 50 interphase cells analyzed. Demonstration of genetic etiology of MKS requires advanced techniques than conventional karyotyping & FISH.

MKS is a rare genetic disorder characterized by early fetal demise.The diagnostic criteria for MKS is presence of at least two of the three classic features like cystic renal dysplasia, occipital encephalocele, and polydactyly, which are observed in 100%, 90%, and 83.3%, respectively. Meckel-Gruber syndrome is a lethal disorder. Most infants are stillborn or die in hours or days after birth. A few patients sometimes survive a few months with poor quality of life. In 1995, Paavola reported another atypical case of a long survivor who died at 18 months of life. Chromosome analysis is essential to exclude trisomy 13, which mimics Meckel-Gruber syndrome. Trisomy 13 carries a 1% recurrence risk, as opposed to the 25% recurrence rate for Meckel-Gruber syndrome. The mortality is 100% and most babies die in utero or shortly after birth. Pulmonary hypoplasia is the leading cause of death. Other causes include liver and renal failure.

Trans-abdominal ultrasonographyperformed at 10–14 weeks gestation, has been shown to successfully detect several of the fetal anomalies associated with MKS, including polycystic kidneys (from 9 weeks gestation), occipital encephalocele (from 13 weeks), and polydactyly (from 11 weeks), in both high-risk and low-risk pregnancies (7). Prenatal diagnosis is also possible by using a combination of these imaging techniques, α-fetoprotein testing of amniotic fluid, and DNA testing of fetus and parents. For example, elevated levels of maternal α-fetoprotein during antenatal screening may be associated with MKS.

The case we encountered has all the features of MKS & is being reported for its rarity.

This case report can be accessed by copy pasting the below link :https://link.springer.com/epdf/10.1186/s42047-020-00062-3?author_access_token=Igu21XnwbY8WU_rQQn5zdm_BpE1tBhCbnbw3BuzI2RMgqLgqEUWIR1lOyrYPq_ AO52K3t MjG Pu9csEYCqa_Hcqza8 EFLKUPZ KOQ3 RFC9V tS9VQ1pOzO3 2CaayOi FbjV5E xJQg 9nzqvyL1_GO9bMK9g==

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2. Lipoma with AHLE (Angiolymphoid hyperplasia with eosinophilia)- A case discussion.

Dr. Anita Shobha Flynn ZTC – Karnataka & Lab head RRL, Bengaluru

Clinical Details:

- A 65 year old male patient presented with a swelling over the back for the last 15 years.
- It was painless and gradually increasing in size.
- There was no history of previous trauma or allergies or infection. No family history of such a lesion was found. No other co-morbidities were present.

Investigation Findings

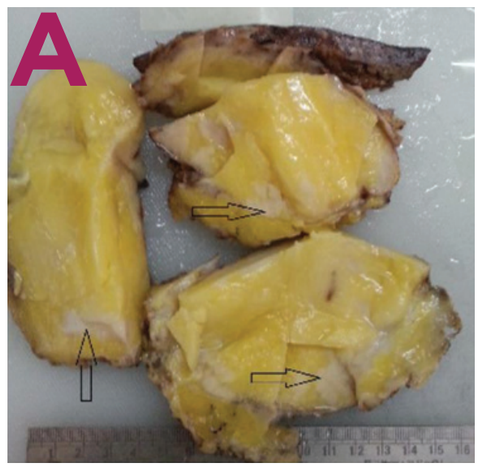
Fine Needle Aspiration Cytology (FNAC) findings showed a lipomatous lesion. Other investigations including eosinophil count were normal. An excision biopsy of the mass was performed and the swelling was excised and sent for Histopathological examination.

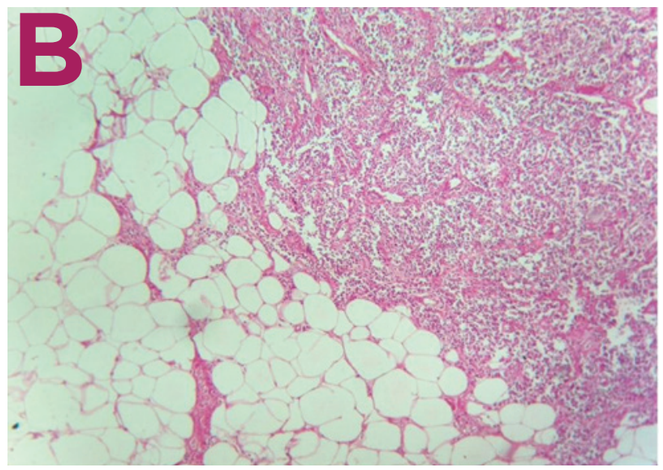
Histopathological examination:

The biopsy was an oval encapsulated yellow soft tissue mass measuring 12 x 11 x 5 cm. An ellipse of skin measuring 11 x 8 cm was present on one aspect. Cut section showed yellow fatty areas with scattered irregular firm grey white areas [A]. Multiple representative sections were taken.

Microscopy showed a benign encapsulated lipomatous tumor composed of lobules of mature fibro-adipose tissue intersected by delicate fibro-vascular septae.

- The blood vessels varied from irregular, poorly canalized, thin walled spaces to rounded well-formed vessels with thickened walls. Vascular channels were lined by endothelial cells showing cobble – stoned or hobnail appearance [D].
- The inflammatory component surrounding the vascular channels comprised of an admixture

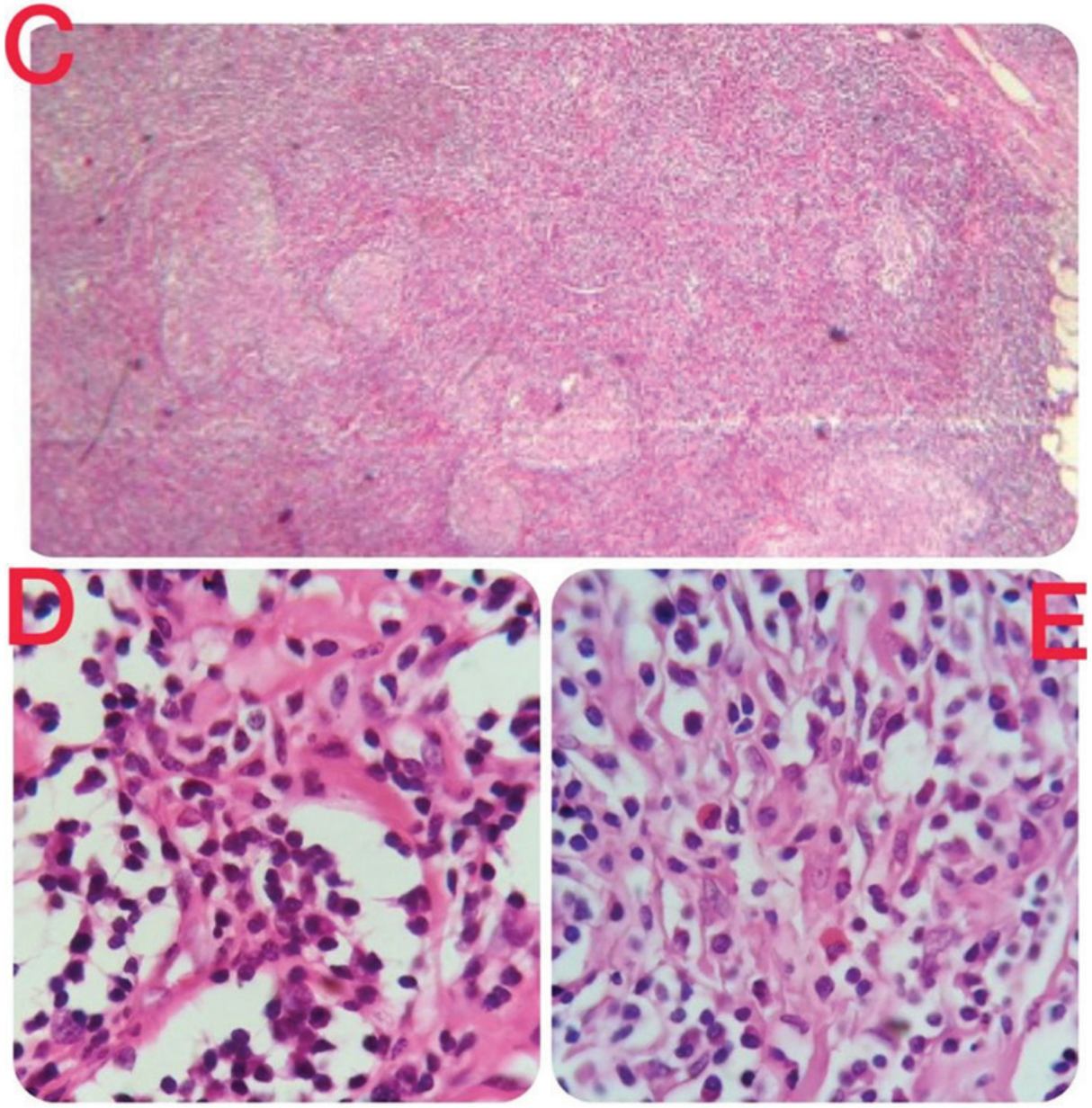




of lymphocytes, plasma cells and few scattered mast cells and eosinophils [E]. At places, lymphoid follicles with ill - formed germinal centres were also noted [C]. There was no atypia seen.

A: Gross picture of encapsulated lipoma with scattered irregular firm grey white areas of ALHE (arrows). B. 4 X , H & E. Lobules of mature adipose tissue with adjacent nodular lymphovascular proliferation

C: 4x, H & E. Lymphoid follicles with ill-formed germinal centres (arrows). D: 100x, H & E. Hobnailed endothelial cells lining vascular channels with interspersed lymphocytes and plasma cells. E: 100x, H & E. Lymphoplasmacytic infiltrate with interspersed eosinophils



The differential diagnoses of Kimura's disease and lymphoma were considered. The former was ruled out due to the paucity of eosinophils, presence of marked vascular proliferation, superficial location and no lymph node involvement in our lesion. The possibility of lymphoma was ruled out because of absence of atypical cells, presence of mature lymphocytes and prominent vascular channels lined by epithelioid endothelial cells. The final diagnosis of Lipoma with an incidental finding of angio-lymphoid hyperplasia with eosinophilia was made.

The patient is doing well on follow up for last 1 year.

Discussion:

Angio-lymphoid hyperplasia with eosinophilia is a benign vasoproliferative disease, the etiology of which is debatable (1).

- A history of preceding trauma or infection is found in 9% of the cases (2).
- Median age of involvement is between second and 4th decade (1, 3).
- Females are more often affected (3).
- It is more commonly seen in the Asian population (1).

The lesions may be solitary or multiple and are characterized by smooth surfaced, red to brown papules or nodules with diameters between 0.5 – 3.0 cm (1,4). These lesions at times may be multilobated and poorly delineated [5, 6]. Our case is a rare presentation of ALHE occurring as multiple nodules within a lipoma over the upper back. Microscopy showed nodular lymphovascular lesion comprising of a proliferation of blood vessels with thickened walls. The vessels were lined by plump (epithelioid) endothelial cells exhibiting a "cobble–stone" appearance. A characteristic chronic inflammatory infiltrate comprising of lymphocytes, plasma cells, histiocytes and eosinophils was seen in the perivascular and interstitial tissues. Eosinophil's account for 5 – 15% of the infiltrate but rarely, may be seen up to 50%. Focal lymphoid follicle formation is also noted (3,7,8).

ALHE has been a controversial lesion with regard to its classification and its relationship to Kimura's disease. However, recent studies have shown that clinical and histologic differences between the two entities support their existence as two distinct clinic pathologic entities (8,9). Kimura's disease is seen more in males and in Asians. It is often associated with regional lymphadenopathy and peripheral eosinophilia and characterized by larger nodules located more deeply, extending to subcutaneous fat, fascia and skeletal muscle (4,8). Histologically, the vascular component is sparse with minimal epithelioid endothelial changes. The inflammatory component is chiefly lymphoid with eosinophils and eosinophilic microabscesses (4,8). ALHE, on the other hand, does not, or rarely, affects lymph nodes. Peripheral eosinophilia is not common and the lesions are more superficially situated in the dermis or sub-cutis (8). The vascular proliferation is prominent with epithelioid endothelial cells and a variable admixture of inflammatory cells [8].

Treatment options range from intra – lesional injections of isotretinoin, glucocorticoids, interferon-2α, and cytotoxic agents to irradiation. However, surgical excision remains the treatment of choice with follow – up as recurrence rate up to 33% is seen due to the multilobation and poor delineation of the lesions (5).

Conclusion:

This is a rare occurrence of Angiolymphoid hyperplasia with eosinophilia occurring in a lipoma. The entity was masked as it occurred multifocal in a lipomatous tumor. The surgeon and the pathologist did not anticipate this entity on clinical or FNAC examination as in both, the lesion had presented as a lipoma. Therefore, this is an interesting case which brings to our knowledge another unusual site in which ALHE can occur.

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ARTICLES

3. Is C-reactive protein (CRP) test a good indicator of inflammation?

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1. Introduction:

C-reactive protein (CRP) is a homopentameric acute-phase protein (115-kDa) made by the liver. It binds exclusively to phosphorylcholine in a Ca2+-dependent way under the control of interleukin-6 (Figure 1). When the body is experiencing inflammation, its levels rapidly increase. CRP levels are typically less than 0.9 mg/dL (mg/dL) in normal individuals. CRP level can be impacted by numerous variables.A CRP test result between 1.0 and 10.0 mg/dL is often regarded as a moderate increase.

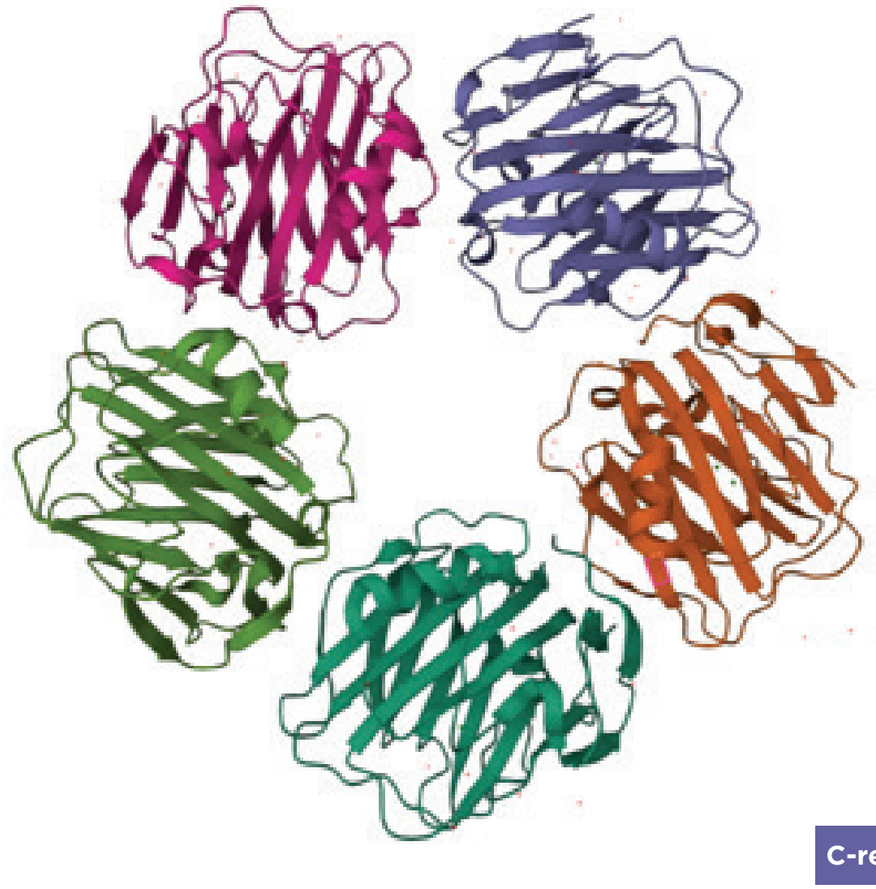

Figure 1: Structure of Human C-Reactive Protein (3PVO) (Source: PDB DOI: 10.2210/pdb3PVO/pdb).

CRP is considered an inflammatory marker and it is a part of the body's fight against illness or injury. Your doctor might order a CRP test to check for infection if you have symptoms of inflammation such as fever, chills, redness or flushing, nausea, vomiting, rapid breathing, and/or rapid heart rate (Figure 2).

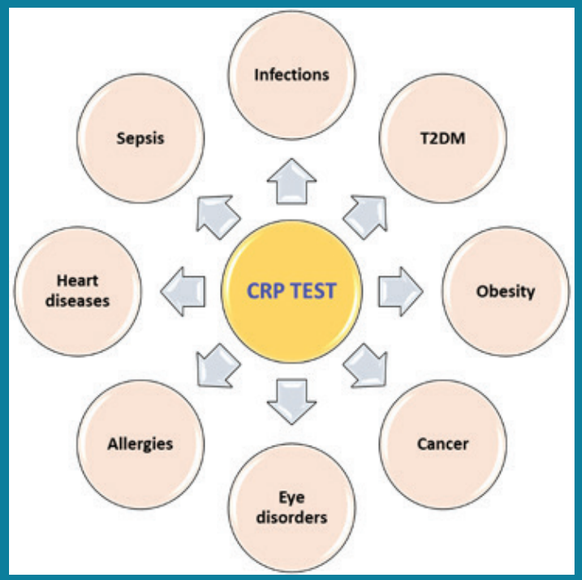

Figure 2: Indications of CRP test for diagnosing different clinical conditions.

2.Risk factors

An elevated level of CRP of more than 10 mg/dL is typically regarded as significant elevation and this outcome could mean any of the pathophysiological situations such as acute bacterial infections, viral illnesses, vasculitis, tumors and trauma. Although a modest elevation has also been linked to a number of non-inflammatory illnesses involving cellular distress or injury, an increase in CRP is typically thought of as a humoral marker of inflammation. Several factors such as the following also contribute to a propensity for developing inflammation.

Age:Increasing age (in both males and females).

Gender:Males often get more heart attacks even though females have a higher mortality rate.

Inheritance:Heart disease is more likely to affect children whose parents already have it. A higher risk may exist for African-Americans, Mexican Americans, Native Americans, Native Hawaiians, and some Asian Americans.

Other contributing factors include diet, smoking, blood pressure, cholesterol, physical activity, diabetes, and obesity. In general, medical professionals advise using this test if you have a moderate chance of having a heart attack within the next 10 years.

The erythrocyte sedimentation rate (ESR) and CRP are among the oldest laboratory tests still in use. Both blood tests are used to identify inflammation. Inflammation can present as either acute (injury or infection) or chronic form. Numerous cells are involved in the release of inflammatory mediators, which result in pain & other inflammatory sequelae described by Celsus. These two tests can serve as both indicators of the presence of pain and inflammation as well as indicators of the efficacy of treatment because pain and inflammation are frequently linked.

Conditions Linked with High CRP: Marker of inflammation?

It is well known that high CRP is typically linked in the pathogenesis of several chronic diseases such as atherosclerosis, metabolic syndrome, obesity, age related macular degeneration, IBD & connective tissue disorders. Interestingly, trans-fat consumption is also related to high blood levels of CRP. Elevated levels of CRP are also implicated in depression & dementia posing the necessity to probe into the role of CRP in neuronal damage.

3.Conditions Linked with Low CRP

In general, low CRP is beneficial. Low CRP levels may contribute to the development of lupus. This is due to the possibility that CRP protects against autoimmunity by binding to cellular waste and auto antigens, which helps clear dying cells. If damaged and dying cells aren't cleared away by macrophages, their waste products build up in various tissues.

4. CRP in inflammation

Patients with high CRP concentrations are more likely to develop stroke, myocardial infarction, and significant peripheral vascular disease. CRP can be used as a very approximate proxy for the risk of cardiovascular disease because it is a generic, nonspecific marker for inflammation and infection.

An increased high-sensitivity CRP (Hs-CRP) level can be caused by a variety of variables; hence it is not a very accurate prognostic marker. However, compared to CRP levels below 1 mg/L, a CRP level of 2.4 mg/L has been linked to a doubled risk of coronary events.

Numerous inflammatory biomarkers with increased levels have been linked to the prediction of negative cardiovascular outcomes. Several studies show that patients with acute coronary syndrome have predictive CRP concentrations.

According to studies, a myocardial infarction, stroke, peripheral vascular disease, and sudden cardiac death may all be predicted by a single increased hs-CRP measurement. To provide further information about the risk of heart disease, it may be used in conjunction with other tests like a lipid panel or with other cardiac risk indicators, such as a relatively new test for the biomarker lipoprotein-associated phospholipase A2 (Lp-PLA2). Troponin-I and creatine kinase isoenzyme (CK-MB), which are mostly produced in cardiac muscle cells, are two common biomarkers of CVD.

Although both Troponin-I and CK-MB can be found in the blood during severe ischemia, cardiomyocyte degeneration, and necrosis, they lack the sensitivity to find even the smallest amount of cardiomyocyte damage. CRP may be somewhat raised in the early stages of myocardial vascular inflammation and is the biomarker that most closely predicts future cardiovascular events. CRP, pro-inflammatory cytokine is linked to worse outcomes following ischemic stroke and a higher chance of stroke risk. Hs-CRP levels > 1.5 mg/dL at discharge are a predictor of subsequent vascular events (transient ischemic attack, cerebrovascular accident, myocardial infarction, unstable angina) and/or mortality. Patients with acute ischemic stroke who have higher CRP levels typically have greater infarct sizes (2,3).

The association between levels of CRP and the incidence of diabetes mellitus suggests a role for inflammation in the etiology of diabetes mellitus. Type 2 diabetes mellitus (T2DM) is a condition that has a high mortality rate and morbidity rate. CRP (also tumor necrosis factor-alpha, and IL-6) is triggered by the excessive adipose tissue to activate insulin signalling pathways, causing insulin resistance that eventually leads to T2DM. Higher haemoglobin A1c (HbA1c) levels are significantly connected with higher CRP levels in elderly T2DM patients (4).

Neurodegeneration of the photoreceptor-retinal pigment epithelial complex leads to age-related macular degeneration which is also known as an acquired disease of the macula (progressive visual impairment). The pathophysiology of age-related macular degeneration is known to be heavily influenced by chronic inflammation. An obviously increased CRP level was found in the exudative type of age-related macular degeneration compared to the early phase. The risk of exudative age-related macular degeneration strongly correlates with higher CRP levels. In addition, elevated CRP levels may cause the activation complement system at the retina/choroid interface, resulting in persistent inflammation and subsequent tissue deterioration.

According to clinical findings, CRP is a key player in the pathogenesis of age-related macular degeneration and can be utilized to gauge the severity of degeneration. Although plasma levels of CRP are independently linked to the risk of age-related macular degeneration, it is unclear whether these relationships are causative or whether CRP only

serves as a marker for age-related macular degeneration (5)..

The increase of CRP is due to a rise in the plasma concentration of IL-6, produced predominantly by macrophages (1) and adipocytes. During the acute phase response, CRP levels increased rapidly within 2 hours of acute insult, rise above normal limits within 6 hours, and peaked at 48 hours. With a resolution of the acute phase response, CRP levels decline with a half-life of 18 hours. CRP can rise up to 50000-fold in acute inflammation, such as during an infection. Its level is mainly determined by its rate of production because of its constant half-life. One exception is that the CRP elevations in the absence of clinically significant inflammation can occur in renal failure (3).

In the initial stages of hemorrhagic stroke, it is believed that mechanical damage in the underlying and surrounding tissue is followed by ischemia, cytotoxic, and inflammatory alterations. The different inflammatory biomarkers and growth factors that are released following intracerebral hemorrhage have drawn more attention in recent years from researchers. C-reactive protein (CRP), Tumor necrosis factor-α (TNF-alpha), homocysteine, and vascular endothelial growth factor were the biomarkers examined in this study. In cerebral hemorrhage, higher CRP is linked to 30-day mortality and an additional 8% rise in cerebral hemorrhage score accuracy (6)..

5. Do conditions affect CRP and ESR

The CRP test is often performed with another blood test called the ESR as a screen to understand if there is concurrent inflammation or to monitor response to treatment. Both ESR & CRP are non-specific markers for inflammation but, together, can offer important clues as to what is going on in the body.

The main difference between the two tests is that changes occur more quickly with CRP. For instance, CRP may drop to normal levels quickly once an infection has cleared, while ESR will remain elevated. In such cases, the ESR can help reveal the “footprint” of an illness even as the symptoms resolve (1,3,5).

Limitations of CRP Test

The agglutination reaction’s intensity is not a reliable indicator of the CRP. Weak reactions may arise with slightly raised or noticeably higher concentrations. Prozone phenomenon (antigen excess) may cause false negatives.

It is advisable, therefore, to check all negative sera by retesting at a 1:10 dilution. Reaction times longer than specified may produce apparent false reactions due to a drying effect.

Strongly lipemic or contaminated sera can cause false positive reactions. Only serum should be used in this test.

A quantitative titration procedure on positive specimens is required to observe increasing or decreasing levels. Patients with high titres of rheumatoid factors may give positive results.

6. Discussion

The CRP test only requires a simple blood draw. The test cannot tell you why or where inflammation is occurring, but it can point to possible causes. The Hs-CRP is a variation of this test used to predict the risk of heart attack or stroke. Phosphocholine is expressed on the surface of several bacterial cells, including pneumococcus bacteria, and CRP binds to it. Triggering the complement system encourages macrophage phagocytosis, which eliminates germs and necrotic and apoptotic cells. Increasing levels of IL-6, which are produced by adipocytes and macrophages in response to a variety of acute and chronic inflammatory conditions like bacterial, viral, or fungal infections; rheumatic and other inflammatory diseases; malignancy; and tissue injury and necrosis, cause this so-called acute phase response (2,7). These circumstances lead to the release of interleukin-6 and other cytokines, which set off the liver’s production of CRP and fibrinogen. Phosphocholine on microorganisms is where CRP binds. It is believed to aid in complement binding to foreign and injured cells and to improve opsonin-mediated phagocytosis by macrophages, which express a CRP receptor. It functions as an early line of defence against pathogens in innate immunity.

Even asymptomatic patients with elevated CRP levels may be harbour occult cardiovascular disease, according to a few modest cross-sectional and case-control studies. The Multiple Risk Factor Intervention Trial (MRFIT) studies was the first prospective study to report the relationship between CRP and coronary disease in asymptomatic, but high-risk men. Increased CRP levels in this 17-year trial had a direct correlation with mortality. CRP levels and the risk of MI and stroke in healthy men were linked in the Physicians’ Health Study, a randomised, double-blind trial of aspirin and beta carotene therapy for the prevention of cardiovascular disease. It is interesting to note that risk reduction is correlated with CRP levels when smouldering endovascular inflammation is controlled with aspirin therapy (8,9).

The extrinsic blood coagulation cascade, the fibrinolytic system, and blood platelet function all appear to be significantly regulated by CRP. CRP heightens the thrombotic response to vascular damage (10). CRP appears to represent a key mechanistic relationship between inflammation and thrombosis because inflammation up regulates CRP expression. CRP structure and biological activity are controlled by the activation of the blood clotting system, specifically platelet activation. As a result, there is bidirectional interaction between inflammation and thrombosis which is dependent on CRP. Be aware that a high CRP level may not always indicate a medical issue requiring treatment. One in twenty healthy individuals will have findings that are not within the usual range. Your healthcare provider will inform you whether additional tests are necessary to determine the cause of the abnormal level.

It is a gold standard predictor of measures of inflammation. There are other ways to measure inflammation, but a study in the March 23, 2000, New England Journal of Medicine (Ridker et al., 2000) concluded that C-reactive protein was a better predictor of cardiovascular events (heart attacks, strokes, bypass surgery, or angioplasty) than other inflammatory markers (10).

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4. Light at the end of the tunnel – Increasing survival rates in brain cancers

Dr.Marquess Raj - – ZTC – Tamil Nadu & Pondicherry

The following write up does not attempt to cover the entire range of CNS neoplasms, shedding light on every miniscule detail & rare entity pertaining to histopathology. Given is a rather concise brief of the 'most common' lesions encountered in the CNS & recent advances that have taken limelight in the last decade.

Five-year relative survival for all malignant brain tumors combined, increased between 1975 to 1977 and 2009 to 2015 from 23% to 36%, with larger gains among younger age groups owing to recent advances & predictive markers available for CNS neoplasms(1).

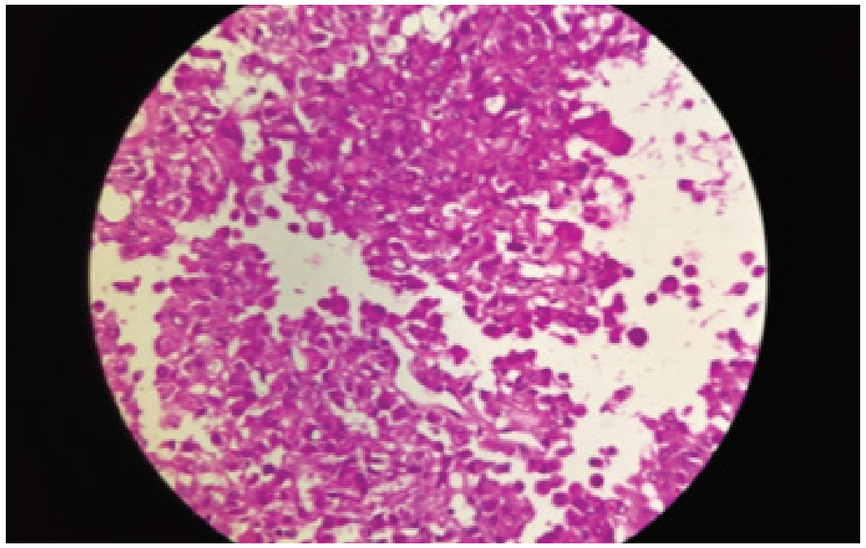
These advances are not mere 'exam questions', but actually are of value to the neurosurgeon & our patients through whose suffering we learn.

Brains for thought:

Study of the central nervous system evokes awe to say the least. Every tiny movement & sensation, either pleasant or unpleasant is mapped in specific regions in the brain. The study of neurons could remind one of space & leave us bewildered. Millions of branching neurons & synapses fuelled by a cocktail of chemicals that still are being studied & understood.

The study of the tumours of the nervous system is incomplete without knowing the cell of origin of the corresponding tumour. It is worth our while to remember that neural tissue & skin develop from the same precursor cells, the neuroectoderm during embryogenesis. Primitive neuroectoderm is the source for tumours such as medulloblastoma, pineoblastoma & retinoblastoma, which are classified under the umbrella term PNET's (primitive neuroectodermal tumours). Misplaced embryonic rests of odontogenic epithelium which transform into tumours carry the intriguing sematic of craniopharyngioma.

Many tumours of the CNS tend to have a genetic link & are often a part of familial cancer syndromes. Study of the presence of these genes in susceptible families & will help physicians mitigate risk & improve outcomes.



Pituitary adenoma showing typical morphology. Genetic praobing investigations can help exclude MEN syndrome.

Immunohistochemistry is only the tip of the iceberg when it comes to CNS neoplasms:

Interestingly enough GFAP which stains the glial tumours astrocytomas&Oligodendrogliomas, also stains normal retinal epithelium(2). The markers used to narrow down brain tumours to glial lineage have grown by leaps & bounds in the last decade.

ATRX, IDH (Isocitrate dehydrogenase), p 53 & 1p19q deletion when added to the arsenal, help differentiating astrocytomas from Oligodendrogliomas. 1p19q deletions are pathognomic of Oligodendroglioma (In medicine, there are always exceptions). This mutation cannot be demonstrated by IHC. Cytogenetic or molecular methods are required for 1p19q deletion demonstration. Presence of 1p19q deletion is associated with a good prognosis.

Aside from codeletion of 1p/19q, oligodendroglial tumors are strongly associated with mutations of IDH1/2, TERT promoter (TERTp), methylation of MGMT and upregulation of PDGFRA. Of these mutations, demonstration of methylation of MGMT promoter in glial tumours has gained importance in recent times. Patients with MGMT promoter respond to alkylating agents such as temozolomide. In a handful of patients temozolomide therapy is faced with resistance much alike finding more darkness at the end of the tunnel (3)..However this does not dilute the importance of targeted therapy & predictive biomarkers in brain tumours. A good example of the same is BRAF V600E mutations in PXA (pilocytic xanthoastrocytoma) & gangliogliomas being targeted by the use of monoclonal antibodies Vemurafenib & Dabrafenib.

Diagnosis of Dural based tumours:

Meningiomas are the most common dural based tumour seen in practice. It is important to remember that meningiomas have more than a dozen variants. Diagnosis as well as grading could be challenging with uncommon variants. EMA & STAT6 are 2 IHC markers that can be put to use in a scenario when it is difficult to narrow down whether the tumour is a fibrous variant of meningioma or solitary fibrous tumour.

CNS tumours & underlying mutations:

It is common knowledge that many CNS neoplasms are associated with familial syndromes (E.g. VHL, Gardner syndrome, etc.). However there are specific mutations that are associated with distinct tumour types. This is an area wherein the geneticist's expertise should be harnessed. A few exam worthy examples are given below:

- Atypical teratoid /rhabdoid tumour: Inactivation of INI1
- Meningioma: Chromosome 22 loss
- Olfactory neuroblastoma : Chromosome 1p deletion
- Medulloblastoma: Isochromosome 17 q

Afterword:

Interpretation of CNS neoplasms requires multi-disciplinary approach. The clinical findings can point towards certain tumours. Example: Seizures are noted in DNET & PXA. Information on location of the tumour is indispensable. Ependymomas are likely to occur in the peri-ventricular location. Presence of a cyst with mural nodule on MRI narrows down the diagnosis to PA, PXA, Hemangioblastoma or ganglioglioma.

It should also be noted the survival rates of patients following the diagnosis of a CNS neoplasm has improved with application of the advances given in this write up. As new entities (such as PLNTY) continue to crop up the latest edition of the WHO blue book for CNS tumours, it should not be forgotten that infective conditions such as TB & cryptococcosis can present as SOLs & simulate neoplasm (4).

References:

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5. Sonnet & a quiz – Shift to the left

Dr.Shalini Singh - Co-editor AD express

Jewels that adorn crimson blood,
Shades that darken if besotted,
By bug or bite or dainty pollen,
Flowing fortresses in crimson blood.

Sprouting cell lines from dark marrow,
Defenders against disease & sorrow.
Bespectacled eosinophil of scarlet tint,
Parasites most will not have a hint.

Monocytes with cytoplasm of ocean hue.
Numbers that increase as the years
roll through.
Round lymphocytes with granules scant.
To dodge them, most viruses can't.
Tiny minions in a tube walled sea,
Prosaically abbreviated to WBC.

Match the following (Same option can be used multiple times)

1. Filariasis	A. Basophil
2. Elevated IgE	B. Leukopenia
3. Supravital staining	C. Metamyelocytes
4. Typhoid	D. Eosinophilia
5. Toluidine blue	E. Reticulocytes

Answers to the pervious quiz in the May 23 issue:

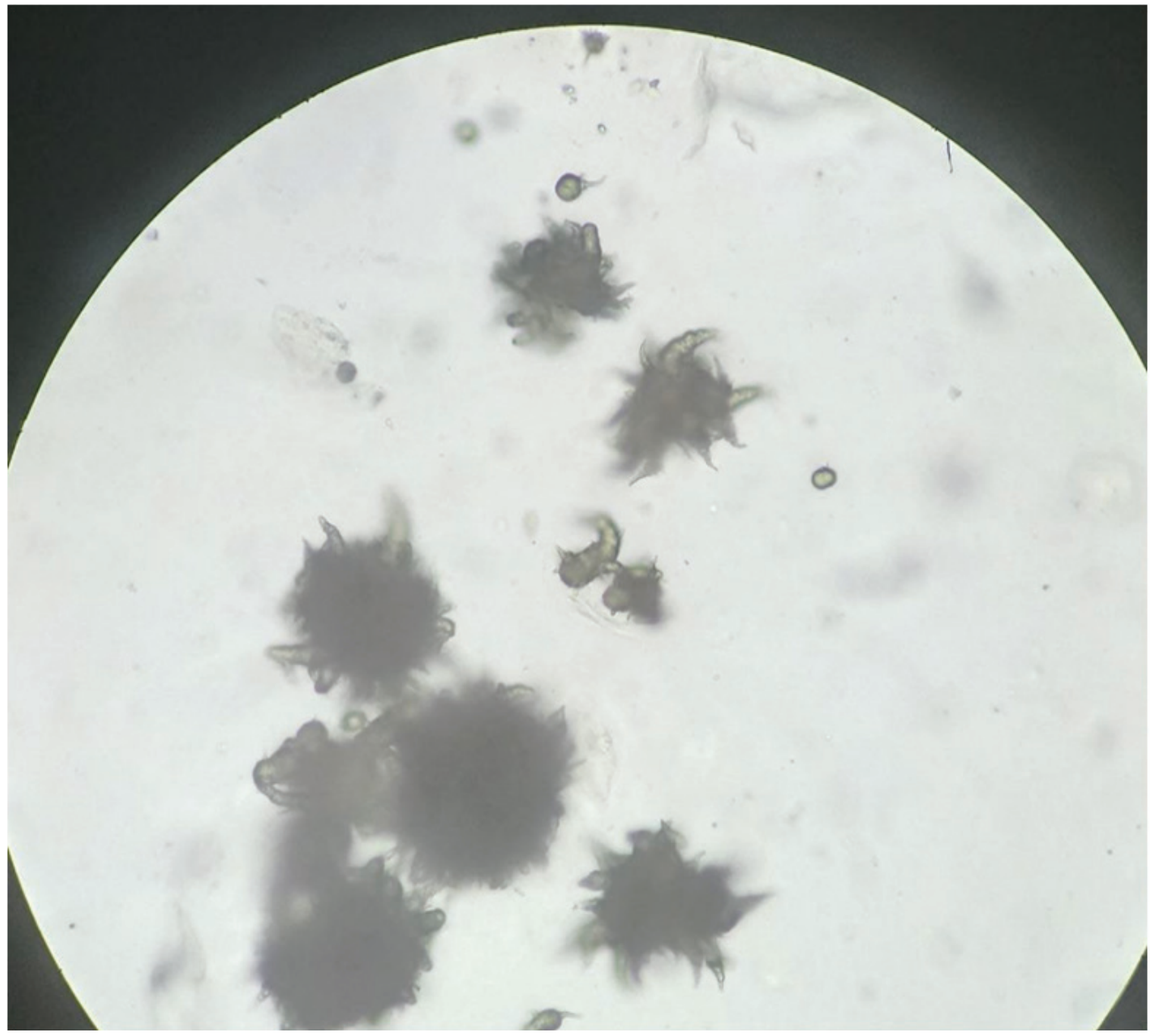
The appropriate 'markers' are matched with the corresponding male accessory sex organs).

1. Fructose	A. Seminal vesicle
2. Total Zinc	B. Prostate
3. Total acid phosphatase	C. Prostate
4. Alpha glucosidase	D. Epididymis
5. Carnitine	E. Epididymis

6. Quiz - – Know your crystal: An uncommon gemstone in a common sample

Dr. Ramesh Kinha - GM, Technical, Apollo Diagnostics

Identify the crystals shown below. A brief of the same shall be given in the next issue.



Answer to identify the cell in the April issue: Prolymphocytes

Prolymphocytes are medium-sized cells with vesicular nuclei and prominent nucleoli.

It is a cell in an intermediate stage of development between a lymphoblast and lymphocyte.

Clinical Significance:

Prolymphocytosis is a condition in which there is an increase in the number of prolymphocytes in the blood. This can occur in certain types of leukemias, such as prolymphocytic Leukemia.

In these cases, prolymphocytosis can be a marker of disease progression and is used to monitor the response to treatment.

CME and Conferences Conducted

Apollo Fertility CME, Greater Noida

Topic:

1. Recent Advancements in IVF with New ART Law
2. HPV genotyping and detection on Sanger Sequencing

Speaker

Dr. Malti Madhu and Dr. Pranav Gupta

AMOGS Conference, Nashik

Topic:

Conference by Obstetric and Gynaecological Society

Apollp Cradle CME, New Delhi

Topic:

1. NIPT
2. Role of PLGF in first trimester screening of Pre-eclampsia and 1T Quad
3. Role of TB-PCR and Genexpert in Clinical Diagnostics

Speaker

Dr. Aanchal, Dr. Anita Kaul, Dr. Tanish Mandal and Dr. Pranav Gupta

Apollo Cradle CME, Karapakkam

Topic:

RPL and BOH

Speaker

Dr. Divya Ambigai and Dr. Marquess Raj

Tripura Medical College RTM

Topic:

HPV/NIPT /MARKERS

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