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THE VARANASI HEMATOLOGY GROUP NEWSLETTER

Thrombotic Thrombocytopenic Purpure (TTP), is not an Easy Diagnosis.

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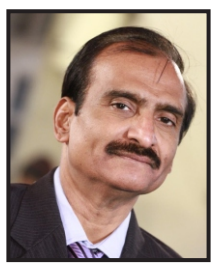

There is tremendous progress and clarity now on Thrombotic thrombocytopenic purpure (TTP) in its pathogenesis, genetic cause, management and prognosis. However, the initial suspicion of the disease is still not easy and many err in diagnosis. Thrombotic microangiopathies (TMAs) are pathological conditions characterized by generalized microvascular occlusion by platelet thrombi, thrombocytopenia, and microangiopathic hemolytic anemia. The prompt recognition of TTP is essential because the disease is fatal in 90% of cases without therapeutic plasma exchange (TPE) or plasma therapy.

TTP is very heterogenous in its presentation, some presenting with severe neurological symptoms mimicking neurological diseases (Cerebro Vascular Accident (CVA) / TIA, Seizure). Administration of *thrombolytic drugs early within 90 minutes is important in CVA but to TTP patients* misdiagnosed as TIA/ Stroke will be detrimental. Review of peripheral blood smear for evidence of hemolysis and RBC fragmentation are so important, which is unlikely to be asked by neurologist in such a case. Cases of TTP mimicking acute myocardial infarction or acute abdomen are also reported (1,2). About 10% TTP patients present with mild abdominal pain. HELLP syndrome with Pre-eclampsia (Hemolysis, Elevated Liver enzymes, low Platelet count) is another condition misdiagnosed as TTP. HELLP syndrome presents with DIC features such as deranged coagulation tests with reduced fibrinogen levels, where as TTP is essentially platelet activation & platelet thrombi presenting with moderate to severely low platelet count. Fever and neurological symptoms are missing in HELLP syndrome. TTP cases have circulating"unusually large" (UL) multimers of von Willebrand Factor (VWF), which mediate adhesion of platelets to vascular endothelium.

The teaching of PENTAD as diagnostic of TTP is not correct, as fulfilling pentad does happen in other conditions such as catastrophic APLA and Hemophagocytic lympho-histiocytosis (HLH) as well. Commonly TTP patients present with dyad (thrombocytopenia with MAHA) or triad (thrombocytopenia, MAHA & renal insufficiency).In a study with hereditary TTP cases (all with <5% ADAMTS13 deficiency) neurologic abnormalities were present in 13 (59%), vomiting, diarrhea in 6 (27%), abdominal pain in 6 (27%), chest pain in 3 (14%), hematuria in 2 (9%), and menorrhagia in 1 (5%) patient.

Many malignancies (particularly adeno-carcinoma of pancreas, lung, prostate, stomach, colon, ovary, breast present late and are diagnosed when already spread throughout body and primary site is not easy to locate (3). Malignancy is one important secondary cause of TTP. TTP and SLE share all the PENTAD presenting features (4, 5). Even malignant hypertension has been misdiagnosed as TTP (6). Cases presenting with marrow necrosis also mimic TTP (7).

Novel successful approaches to treatment of TTP include infusions of recombinant ADAMTS13 and plasma cryo-supernatant or solvent-detergent treated plasma as a source of the exogenous protease.

Preliminary investigations in suspected cases of TTP must include Hemogram with peripheral smear examination, renal function tests, LDH, Coombs's test and investigations for DIC. ADAMTS13 activity or antigen assay is a confirmatory test. Reduced values are seen in sepsis, liver disease, pregnancy, malignancy, but severe deficiency <5% is diagnostic of TTP. Anti ADAMS13 antibodies (IgG type) is another important investigation to detect Non-familial acquired TTP. ELISA methods have been used for quantitative estimation of ADAMS13 assay as well as ADAMS13 IgG antibody assay. An accurate and timely diagnosis is critical for a successful outcome in TTP.

Hereditary TTP (also called Upshaw–Schulman syndrome) is the result of compound heterozygous or homozygous mutations in the ADAMTS13 gene (synthesised in liver) & represent 10% of all cases of TTP. Majority of these cases present with TTP early age in neonatal or childhood, though 20% cases present in adulthood. Hereditary TTP is caused due to deficiency in the von Willebrand factor cleaving protease which is ADAMTS13 (A Disintegrin And Metalloprotease with Thrombospondin type 1 motif, 13th member of the family). Congenital TTP (cTTP) cases are very rare (1 case per million person years) and represent approximately 10% of all TTP cases. Based on reported congenital TTP case reports, 48% of patients develop TTP in the neonatal period, 31% during childhood (2 months to 18 years) and 21% during adulthood.

Acquired non-familial TTP is an immune-mediated, non-familial form of TTP that accounts for the majority of cases (from 60% to 90%) as acute idiopathic or sporadic TTP. They have severe ADAMTS13 deficiency as a result of circulating autoimmune anti-ADAMTS13 autoantibodies either inhibiting ADAMTS13 activity or enhancing ADAMTS13 clearance. The ADAMTS13 cysteine-rich and spacer domains have been shown to be the primary autoimmune targets. The antibodies are transient; they usually disappear from the circulation when remission is achieved by effective treatment and this occurs with the normalization of ADAMTS13 activity in remission phase.

Acquired/ secondary TTP (about 40% cases) is defined as those with a primary disease such as drug toxicity (quinine, cyclosporin, calcineurin inhibitor, mitomycin, ticlopidine and clopidogrel), infection, cancer, transplantation, & ADAMS13 is not involved in its pathogenesis. The mechanism of secondary TTP is poorly understood, and a probable aetiology may involve endothelial damage. Plasma therapy is not very effective. Pregnancy is a prominent risk factor for the development of TTP. Pregnancy associated TTP is reported to represent 5-10% of all adult TTP cases.

Up to now, plasma therapy is still conventionally considered the gold standard for the treatment of all forms of TTP. It may be plasma exchange, recombinant purified ADAMTS13 is most effective treatment, which has recently cleared clinical trials and is available for TTP patients. Novel successful approaches to treatment of TTP include infusions of recombinant ADAMTS13 and plasma cryo-supernatant or solvent-detergent treated plasma as a source of the exogenous protease. ■■

What's inside...

VOLUME : 3, ISSUE : 3, April 14, 2022
THE VARANASI HEMATOLOGY GROUP
NEWSLETTER

APPROACH TO METASTATIC TUMORS IN BONE MARROW

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Bone Marrow (BM) examination is essential for diagnosis of disorders of hematopoietic system, but it is also carried out for staging of a significant proportion of non-hematopoietic tumors. Bone marrow involvement is commonly seen in tumors that spread via blood stream. In adults, lung, breast, prostate, kidney, stomach and thyroid predominate. In children, most frequently encountered tumors are neuroblastoma, rhabdomyosarcoma, germ cell tumors, Ewing's sarcoma and other primitive neuroectodermal tumors (PNET) and retinoblastomas. Though other carcinomas, sarcomas and melanomas are less frequently diagnosed, almost every type of tumor has been shown to metastasize to the bone marrow.

Infiltration of the marrow should be suspected under the following conditions (1) Clinical Suspicion of occult malignancy (Bone pain, Pathological fracture, Pyrexia of Unknown Origin) (2) Radiological Suspicion of occult malignancy (Lytic or sclerotic lesions, unexplained hot spots on bone/PET scan (3) Suspicious biochemical investigations (Hypercalcemia, raised serum alkaline phosphatase, raised tumor markers) (4) Presence of Hematological abnormalities

Indications and Objectives of Bone Marrow Biopsy (BMB) in Non-Haematological Malignancies

Detection of secondary spread to bone marrow is important for multiple reasons.

a. For clinical staging; the metastasis of bone marrow by the solid tumors is a sign of advanced stage of disease and poor prognosis.
b. To determine the site of origin by IHC when the primary is unknown
c. Assessing residual hematopoietic reserve.
d. Investigating unexplained cytopenias in the post-therapy period.
e. To modulate and/or add adjuvant therapies.

The iliac crest is a large bone which remains hemopoietically active across all age groups; it is therefore an appropriate and preferred site for most BMBs. In cases the tumor deposit is large enough to be detected radiologically, a guided biopsy may be performed.

Peripheral Blood

Most patients with a metastatic deposit in the bone marrow manifest hematological abnormalities. These include (1) anemia, (2) thrombocytopenia, (3) pancytopenia, (4)leukoerythroblastic blood picture and (5) carcinocythemia.

The most common finding is anemia, but it is nonspecific. The types of anemia seen in such patients include anemia of chronic disease, iron deficiency and microangiopathic hemolytic anemia(MAHA). MAHA has been most commonly associated with mucin-producing neoplasms, such as adenocarcinoma of the breast, lung or gastrointestinal (GI) tract, but has also been shown in metastatic sarcoma and tumors of childhood.

Myelopthisic Anemia is a type of BM failure due to replacement of the hematopoietic elements of the BM by metastatic deposit, lymphoma and/or granuloma resulting in pancytopenia.

Carcinocythemia also known as carcinoma cell leukemia is defined as circulating tumor cells (CTCs) in the peripheral blood. It has been described in cases of carcinoma of the breast, lung (small cell) and ovary along with neuroblastoma, Wilms tumor and rhabdomyosarcoma. CTCs is not an absolute indicator of BM involvement or of a metastatic disease, as they are often apoptotic.

Liquid Biopsy involves collection and analysis of blood for circulating tumor DNA/RNA or CTCs. They are being evaluated for molecular profiling, accordingly personalized treatment selection, for monitoring of disease response and resistance, for tracking of minimal residual disease, and for early cancer diagnosis. Liquid biopsies can capture the entire molecular panorama of the tumoral landscape. It allows detection of certain mutations like EGFR, KRAS and BRAF and allows initiation of targeted therapy.

Bone Marrow Biopsy versus Bone Marrow Aspirate (BMA)

Various studies have shown that BMB are more sensitive in identifying metastatic lesions involving the BM as compared to BMAs. Though BMAs are quick, less painful and more economical; BMB with touch imprints is the best way for staging patients as it offers benefits of both histological and cytological evaluation.

The advantages of BMB over BMA include

1. More sensitive for detection of focal lesions.
2. More sensitive in picking up lesions associated with fibrosis, especially adenocarcinomas, which elicit marked desmoplastic reaction and become non-aspirable.
3. Associated bone and stromal changes can be visualized .
4. Multiple sections allow assessment of larger volume of marrow.
5. Serial sectioning also permits use of IHC and other ancillary techniques for determining the unknown primary and other prognostic studies.

Thus histological evaluation of metastatic deposit gives a better idea of tumor morphology, its secondary effects on marrow and evaluation of residual hematopoietic reserve.

Morphology of Metastatic tumors in Bone Marrow Aspirate and Biopsy

Bone marrow aspirate smears can vary from being hypercellular to normocellular to hypocellular and more often than not, because of the associated desmoplastic response, a dry tap may be yielded. Smears may show presence of single scattered cells to epithelial cell clusters with vague glandular formation. These cells are generally larger than hematopoietic cells except small round cell tumors, which may be confused with lymphomas. Associated findings include, necrosis, gelatinous transformation of the marrow, plasmacytosis and presence of osteoblasts /osteoclasts.

Immunohistochemistry (IHC) in Diagnosis of Primary of Metastatic Deposit

Immunohistochemical confirmation of metastasis in a patient with known primary neoplasm is relatively straightforward. However, in the absence of an identifiable primary tumor site, despite extensive multidisciplinary investigations, carcinomas of unknown primary site (CUPs) are characterized as metastatic carcinomas. IHC provides diagnostic guidance in approximately 90% of undifferentiated malignant tumors but involves a fastidious and expensive algorithimic approach based on clinico-radiological data, histomorphology and IHC.

The adult tumors may further be subdivided into carcinomas, melanomas and lymphomas. Vimentin is a non-specific marker, however, a vimentin negative tumor is unlikely to be a sarcoma except alveolar soft part sarcoma. Carcinomas can further be subdivided into three histological subtypes of adenocarcinoma, undifferentiated carcinoma and least common, squamous cell carcinoma. If the metastatic tumor is cytokeratin positive, further CK7 and CK20 can help distinguish the nature of tumor and with the use of a panel of monoclonal antibodies, the site of origin of the primary tumor can be determined.

Paediatric tumors usually present as small round cell tumors. Neuroblastoma cells usually express neuronespecific enolase(NSE) and PGP9.5; less consistently, chromogranin, synaptophysin, Gd2 and the antigens detected by antibodies Nb84 and NeuN are expressed. In rhabdomyosarcomas, immuno-histochemical staining for desmin, myogenin and MyoD1 are usually positive although staining for myoglobin, which is said to be more specific, is variable. The characteristic profile for Ewing's sarcoma includes reactivity with vimentin, CD99 (usually membranous), and FLI1 (nuclear) with variable reactivity for neural markers. ES with (11;22) (q24;q12) expresses CD99 (MIC2) strongly. Blastemal-predominant Wilms Tumor express WT1 and PAX2. Medulloblastoma express synaptophysin and NeuN

Problems and Pitfalls

Despite good morphological assessment and use of ancillary techniques, a subset of cases is misdiagnosed. The causes may be variable like normal components of the marrow can be confusing to the unfamiliar pathologist. Artefactual inclusions, distorted/scanty tissue due to extensive fibrosis and/or necrosis can also lead to misinterpretation/pitfalls. On IHC, aberrant or unexpected expression of markers is an important source of diagnostic error in the evaluation of undifferentiated tumors. Also, poorly fixed sample or decalcification can lead to unpredictable pattern of IHC staining.

Take Home Message

BM examination is a diagnostic method for detecting tumors of the hematopoietic system as well as nonhematopoietic system. Ancillary techniques of cytochemistry, immunohistochemistry and molecular genetic analysis can never substitute the importance of information provided by the clinician, radiology and careful examination of the hematoxylin and eosin slides.

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APPROACH TO LEUKEMIAS

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What is leukemia?

Leukemia can be defined as neoplastic proliferation of hematopoietic elements. They are characterized by diffuse replacement of Bone Marrow by neoplastic cells. This clonal neoplastic population can be of myeloid lineage and lymphoid lineage predominantly. However, WHO provides a comprehensive classification for different types of clonal proliferation ranging from acute to chronic hematopoietic neoplasms, reticuloendothelial cell neoplasms and histiocytic neoplasms. In the current WHO classification, lesions which were previously considered benign eg: Castleman disease, have now been included as malignant lesions.

Leukemias are broadly classified in to acute leukemias and chronic leukemias based on the cell type and state of maturity of leukemic cells. There are two types of leukemias when we come across the general classification

-ACUTE LEUKEMIAS – presence of very immature cells called blast cells. Rapid course.

- Acute Myeloblastic Leukemia
- Acute Lymphoblastic Leukemia

-CHRONIC LEUKEMIAS – well differentiated mature leukocytes are present. Relatively indolent course.

- Chronic Myeloid Leukemia
- Chronic Lymphoid Leukemia

Etiological factors involved in genesis of leukemia

Multiple acquired factors have been implicated in carcinogenesis in general. If we remember the chapter Neoplasia in Robbins we would remember the various boxes highlighting the acquired causes of carcinogenesis. They mentioned viruses, chemical factors like dyes, drugs(chemotherapeutic agents),immune mediated mechanisms,trauma to DNA repair pathway and radiation as common cause of carcinogenesis in any cancer. All these factors affect various receptor mediated as well as direct pathways which in turn affect the cell proliferation and DNA maturation cycles.

In the bone marrow there are 2 main compartments

- The cellular compartment : Erythroid precursors, myeloid precursors, megakaryocytes and precursors, lymphocytes, macrophages, mast cells, plasma cells

- The stromal compartment : Stromal cells, fat cells, blood vessels, fibroblasts, endothelial cells, iron deposits, osteoblasts, osteoclasts

Hematopoietic malignancies arise from the cellular compartment. The stem cell divides into 2 progenitor cell lines the lymphoid and the myeloid progenitor cell lines. While the lymphoid progenitor cell lines mature to committed stem cells which finally form mature T cell, B cell and NK cell the myeloid cell line committed stem cells form RBCs ,platelets and rest of the myeloid cells. Mutation in any step of this maturation leads to leukemia/lymphoma of that specific lineage.

Clinical history

Leukemia as a disease can have variable clinical presentations in both adult and pediatric population. Patient presents to the OPD with complaints of persistent fever, malaise, weight loss and organomegaly. Search for active bleeding, petechiae and growth abnormalities (certain hematological conditions like inherited bone marrow failures may mimic leukemia clinically or hematologically and very sequential examination is required to reach a diagnosis)

Family history for any similar complaints, any co morbidities or rare genetic conditions being repeated in the family should be ruled out.

Rule out past history of any relevant drug therapy or any therapy for diabetes, hypertension etc.

Clinical examination

The routine pattern of examination as taught in MBBS is followed with special stress on abdominal examination for organomegaly, examination of all palpable lymph nodes(cervical,inguinal,axillary,pre auricular, post auricular) to rule out involvement.

Acute leukemias are generally abrupt onset with symptoms related to anemia, thrombocytopenia and frequent infections, Bone pains and tenderness and organ infiltration(generalized lymphadenopathy splenomegaly, hepatomegaly, testicular or CNS involvement. (more common in ALL))

The age of onset is as follows ,ALL-Childhood leukemia, peak incidence- 1-5 years while AML- is in 15-40 yrs. It is well known that> 80% of ALL seen in childhood and > 80% of AML seen in adults. Conditions like inherited bone marrow failures may present with other features like café au-lait spot, thenar atrophy etc. In pediatric patients' skeletal deformities should be carefully searched for.

LABORATORY DIAGNOSIS OF LEUKEMIA WITH EMPHASIS ON ACUTE LEUKEMIA

Hematological investigations : Haematological investigations are a key to diagnose the leukemia

-Complete blood count:

Haemoglobin-decreased,

TLC-leucocytosis commonly seen

DLC-to assess percentage of blasts and other cells

Platelet count-generally thrombocytopenia

Note:

Aleukemic leukemia-The peripheral counts do not show any increase in TLC or evidence of leukemia. Bone marrow is hypoplastic with blasts in such cases.

Sub leukemic leukemia: The peripheral counts are not increased however there is evidence of blasts in the peripheral smear.

-peripheral smear examination: morphology of immature cells to ascertain the type of blast (lymphoblast or myeloblast)

-Bone marrow examination: Hypercellular, reduction in erythroid, myeloid & megakaryocytic precursors, presence of blast, percentage & morphology

-Special stains and cytochemistry - MPO, PAS, CAE, NSE

Other Investigation :

- CSF examination: to assess involvement of CNS by blasts
- *Liver Profile*
- *Renal Profile*
- *S.LDH levels, viral markers*
- Flowcytometry : Routine flowcytometric markers have already been mentioned in the table above. However, flowcytometry is also used in certain other situations like *to assess minimal residual disease*: In marrow on chemotherapy each treatment protocol has specific days on which the marrow is sent to the pathologist to assess the remission status. Sometimes >5% blasts are clearly identified on morphological examination to call a bone marrow "not in morphological remission" however at times the marrow is either hemodiluted, hypocellular or even hypoplastic and there is suspicion of persistent disease. There the role of flowcytometry in detecting 1 leukemic cell/10000 events(0.01%) comes in useful, and the sample is used to obtain the minimal percentage of blast in it.

This helps is further treatment plan of the patient.

Panel of markers used

T-ALL-Co expression of CD3/TdT or CD5/TdT

B-ALL-Overexpression-CD19,CD10,CD34

AML-CD33, Cd13, Cd117, Cd64, HLA-DR, CD34

- Cytogenetics : AML, MDS, AML with recurrent genetic abnormalities, Downs Syndrome associated with AML all these entities have specific mutations which help in diagnosis, treatment and prognosis.EgFLT3/ITD mutation is bad prognosis while CEBPA or NPM1 has better prognosis. Sometimes cytogenetic anomalies have specific morphological presentations like cup shaped blasts in NPM1 mutations.

Aberrant expression of antigens: On flowcytometry leukemic cells may mimic markers for other lineages eg. AML expressing CD2,CD19 or ALL with CD13.However not all expressions have prognostic significance. There is a scoring system proposed for the same to diagnose ambiguous lineage leukemias. Some significant aberrations are

-CD5 expression in B-cells in CLL

-CD13/CD33 on CD10(CALLA) positive B cells

-Abnormal BCL-2 expressions on CD10

Points to be remembered during work up

Acute leukemias are defined as neoplasms with more than 20% blasts in the peripheral blood/bone marrow(WHO).Failure of maturation of leukemic blasts into their functional end cells. Blast cells accumulate in BM, suppress normal marrow element by physical replacement.

There is loss of mature myeloid elements like rbcs, and platelets, manifested by anemia, thrombocytopenias.

- *Blast equivalents*-Cells other than blasts which are counted as blasts are called blast equivalents-

  · *Promonocyte in Monocytic and myelomonocytic leukemia,*

  · *promyelocytes in acute promyelocytic leukemia,*

  · *erythroblasts in pure erythroleukemia*

- FAB defines 3 types of blast cells morphologically

Type 1-undifferentiated,no granules, high N:C,prominent nucleoli

Type 2-Few fine azurophilic granules/auer rods/pseudo chediak higashi granules, slightly low N:C and central nucleus

Type 3-fair number of granules, fine chromatin with central nucleus

-*Hematogones*-Post chemotherapy bone marrow when regenerating shows presence of regenerating immature cells specially seen in ALL. These cells belong to the B cell lineage and mimic blasts morphologically. They can also be seen in other conditions like

· *Autoimmune or congenital cytopenias*

· *Solid tumors like neuroblastoma*

· *lymphomas*

· *Regenerative marrow post infectious supressions, AIDS etc.*

These can be differentiated from blasts by presence of J shaped trail pattern(CD10/CD20) on flowcytometry dot plot. They express the normal maturation pattern for B cells that is Cd34 <TdT <Cd20 <PAX5.

Other categories in WHO Classification are:

-AML with related precursor neoplasms

- AML with recurrent genetic abnormalities
- AML with MDS related changes
- Therapy related AML
- AML NOS-similar to FAB classification
- Myeloid sarcoma
- Myeloid proliferation with Downs syndrome

-Acute leukemia of ambiguous lineages

Few important terms that a pathologist should know when reporting leukemia bone marrows

Treatment failure: when blasts are persisting on in the initial phases of treatment

Relapse: Re-surgence of blast counts after treatment completion with a bone marrow in remission

Tumor lysis syndrome : Cell death due to chemotherapy agent or very high burden of tumor leading to metabolic disturbance in the body {(serum calcium(increased), serum uric acid, serum phosphate (reduced), serum electrolytes, S.LDH (raised)}

Secondary leukemia: Leukemias caused after chemotherapy, more common when solid organ malignancies are treated then the chemotherapy toxicity causes development of secondary leukemia.

Summary: to summarise the key headings while approaching leukemias-

- Clinical features
- PB Examination- Hb, TLC, DLC (% and morphology of blast cells), P/C, GBP
- BM examination- Percentage and morphology of blast cells
- Cytochemistry (AML blasts show MPO positivity, ALL blasts show block positivity for PAS) and Immunophenotyping of blast cells
- Cytogenetics and molecular diagnosis
- WHO classification
- Biochemical tests
- CSF examination – in case of CNS involvement (grading based on cytology and MRI findings)
- Prognosis of ALL
- Differential Diagnosis
- Treatment

General treatment protocols in leukemia (refer to NCCN guidelines)

Leukemia	Therapy protocol
ALL	BFM-95
AML	A-adriamycin B-bleomycin V-vinblastin D-dacarbazine
CML	Tyrosine kinase inhibitors
CLL	B+R
Hodgkins lymphoma	ABVD
Non Hodgkins lymphoma	R-CHOP/CHOP SMILE protocol Treatment defined as per type of lymphoma
APML	ATRA,arsenic

Approach to Metastatic Tumors in Bone Marrow

References :

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References :

SALIENT FEATURES OF AML with RECURRENT GENETIC ABNORMALITY

AML with t(8;21)	1. Granular blasts with perinuclear hofs with large salmon-colored granules
	2. **LARGE** blasts with abundant basophilic cytoplasm with abundant azurophilic granules & **HOF.**
	3. Few blasts with very large granules (pseudo-Chediak-Higashi granules) indicating abnormal fusion.
	4. Frequent Auer rods - single, long and sharp rod with tapered ends. May be detected in mature neutrophils.
	5. Increased normal eosinophilic precursors.
	6. Aberrant CD19,PAX5 expression , CD34+,HLA-DR+ MPO +CD13 +but weak CD33+ on myeloblasts
AML with inv (16) or t(16; 16)	-CBFB-MYH11 mutation -monocytic and granulocytic differentiation -AML M_4 with abnormal eosinophils with basophilic granules -mutation with <20% blasts also considered as AML
AML with inv (3)	Mimics MDS with 5q- { PBS; Platelet count – normal; BM -↑ dysplastic megakaryocytes (monolobated/bilobed nucleus) } Distinction from 5q- Multilineage dysplasia & increased number of small mono or bilobed megakaryocyte
AML with t(9; 11)	• AML 5 in children → Extra medullary myeloid sarcoma. Tissue infiltration (gingiva, skin) • DIC
AML with t(6;9)	Peripheral and BM basophilia .Multilineage dysplasia with basophilia
AML with t(1;22)	AML-M7 type picture
APML with PML-RARA	Bilobed nuclei with blasts lacking HLA-DR & usually CD34-
AML (megkaryoblastic) with t (1;22)	Infant without Down syndrome with CD41+ & CD61 + blasts .CD42blasts + less frequent

DIFFERENTIATION OF AML with BCR- ABL 1 FROM CML in blast crisis

	AML with BCR-ABL 1	CML in blast crisis
1. Clinical	Less frequent splenomegaly	
2. Peripheral blood basophilia	Lower (<2% basophils)	
3. BM		
(i) Cellularity	80%	95-100%
(ii) Dwarf megakaryocytes	Less common	
(iii) Non-blast M:E ratio	Relatively normal	More elevated
4. Outcome	Improved survival with tyrosine kinase inhibitor therapy followed by allogeneic haematopoietic cell transplantation	Death sentence