A DISSERTATION ON

"OCULAR MANIFESTATIONS IN BLOOD DYSCRASIAS"

Submitted to

THE TAMIL NADU DR. M. G. R. MEDICAL UNIVERSITY

In partial fulfilment of the requirements

For the award of degree of

M.S. (Branch III) --- OPHTHALMOLOGY

GOVERNMENT STANLEY MEDICAL COLLEGE & HOSPITAL THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU

APRIL 2017

CERTIFICATE

This is to certify that the study entitled **"OCULAR MANIFESTATIONS IN BLOOD DYSCRASIAS "** is the result of original work carried out by Dr.Suhasini.S, under my supervision and guidance at **STANLEY MEDICAL COLLEGE, CHENNAI.** The thesis is submitted by the candidate in partial fulfillment of the requirements for the award of M.S Degree in Ophthalmology, course from June 2014 to March 2017 at Stanley Medical College, Chennai- 01.

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DECLARATION

I hereby declare that this dissertation entitled "**OCULAR MANIFESTATIONS IN BLOOD DYSCRASIAS**" is a bonafide and genuine research work carried out by me under the guidance of **Professor Dr. K.BASKER M.S. D.O.,** Head of the Department, Department of Ophthalmology, Government Stanley Medical college and Hospital, Chennai – 600001.

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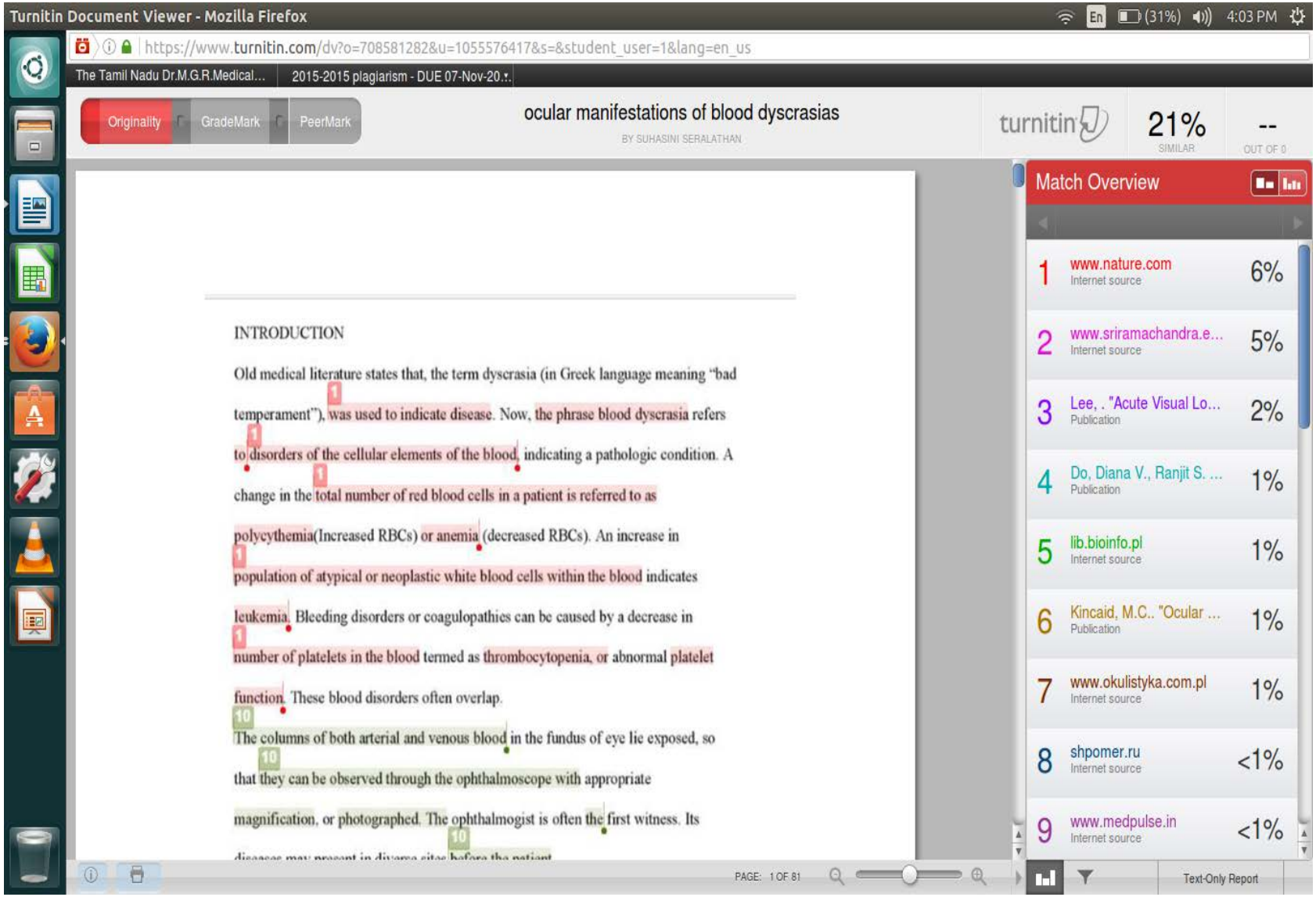
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INTRODUCTION
Old medical literature states that, the term dyscrasia (in Greek language meaning "bad temperament"), was used to indicate disease. Now, the phrase blood dyscrasia refers to disorders of the cellular elements of the blood, indicating a pathologic condition. A change in the total number of red blood cells in a patient is referred to as polycythemia(Increased RBCs) or anemia (decreased RBCs). An increase in population of atypical or neoplastic white blood cells within the blood indicates leukemia. Bleeding disorders or coagulopathies can be caused by a decrease in number of platelets in the blood termed as thrombocytopenia, or abnormal platelet function. These blood disorders often overlap.
The columns of both arterial and venous blood in the fundus of eye lie exposed, so that they can be observed through the ophthalmoscope with appropriate magnification, or photographed. The ophthalmogist is often the first witness. Its
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Title of the Work : Ocular Manifestations in Blood Dyscrasias.

Principal Investigator : Dr. S Suhasini

Designation : PG MS (Opthalmology)

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The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 26.11.2014 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

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K Vasanthin

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PART-I

PART-II

ANNEXURES

ABBREVIATIONS

RBC	:	Red Blood Cells
WBC	:	White Blood Cells
Hb	:	Hemoglobin
Hct	:	Hematocrit
Vit B12	:	Vitamin B12
TNF	:	Tumour Necrosis Factor
IFN	:	Interferon
IL	:	Interleukin
ILM	:	Internal Limiting Membrane
EPO	:	Erythropoietin
SCD	:	Sickle Cell Disease
BM	:	Bone Marrow
ALL	:	Acute Lymphocytic Leukemia
AML	:	Acute Myeloid Leukemia
CLL	:	Chronic Lymphocytic Leukemia
CML	:	Chronic Myeloid Leukemia
HL	:	Hodgkin’s Lymphoma
NHL	:	Non- Hodgkin’s Lymphoma
CBC	:	Complete Blood Count
RPE	:	Retinal Pigment Epithelium
CWS	:	Cotton wool spots

CRVO	:	Central Retinal Vein Occlusion
BRVO	:	Branch Retinal Vein Occlusion
CME	:	Cystoid Macular Edema
ITP	:	Idiopathic Thrombocytopenic Purpura
MM	:	Multiple Myeloma
Ig	:	Immunoglobulin
ICP	:	Increased Intracranial Pressure
CNS	:	Central Nervous System
MR	:	Magenetic Resonance
CT	:	Computed Tomography
VEGF	:	Vascular Endothelial Growth Factor
FGF	:	Fibroblast Growth Factor
cGy	:	Centigray
CN	:	Cranial Nerve
GVHD	:	Graft Versus Host Disease
SCH	:	Sub- Conjunctival Hemorrhage
CF	:	Counting Fingers
PL	:	Perception of Light
Va	:	Visual Acuity
CR	:	Complete Resolution
LP	:	Persistance of Lesions
NF	:	No follow-up
REL	:	Relapse

PART – I

INTRODUCTION

Old medical literature states that, the term dyscrasia (in Greek language meaning “bad temperament”), was used to indicate disease. Now, the phrase blood dyscrasia refers to disorders of the cellular elements of the blood, indicating a pathologic condition.[1] A change in the total number of red blood cells in a patient is referred to as either polycythemia (Increased RBCs) or anemia (decreased RBCs). An increase in population of atypical or neoplastic white blood cells within the blood indicates leukemia.[2] Bleeding disorders or coagulopathies can be caused by a decrease in number of platelets in the blood termed as thrombocytopenia, or abnormal platelet function. These blood disorders often overlap.[1] The columns of both arterial and venous blood in the fundus of eye lie exposed, so that they can be observed through the ophthalmoscope with appropriate magnification, or photographed. The ophthalmogist is often the first witness. Its diseases may present in diverse sites before the patient reaches the haematologist, whose analysis gives the final diagnosis. [3]

NEED FOR THE STUDY

OCULAR MANIFESTATIONS IN BLOOD DYSCRASIAS

The ocular manifestations of blood dyscrasias are frequently observed as indicated by clinical and pathologic studies. The ocular fundus gives an unparalleled direct view of the hematologic effects of blood dyscrasias, apart from the hemorrhagic and infiltrative complications observed in the skin and mucous membranes. The ophthalmologist, by observing the characteristic changes in the retina, may be the first member of the medical team to identify the hematologic effects of a blood dyscrasia.[3]

The typical ophthalmoscopic findings are not pathognomonic of blood dyscrasias and may be observed in many conditions involving the eye (i.e., diabetes, hypertension, collagen vascular disease). However, the distribution and pattern of the retinal findings in blood dyscrasias are characteristic. If these characteristic findings are identified on ophthalmoscopy, then further investigations may reveal a blood dyscrasia allowing for early referral for treatment by the physician.[4]

Our study aims to observe the incidence of the ocular manifestations of blood dyscrasias, their diagnostic and prognostic importance to the disease and the resolution or progression with treatment.

HISTORICAL REVIEW

In the 1860s, Liebreich first described leukemic retinopathy. Since that time, virtually all intraocular structures have been found to become involved. 33 different ocular anomalies were listed by Goldbach from among the 242 leukemias at John Hopkins Hospital; of this majority were seen in the fundus.[2]

Patients have been reported with leukemic infiltrates of the optic nerve, choroid, retina, iris, ciliary body, and anterior chamber. In multiple myeloma, Bronstein reported plasma cells floating free in the anterior chamber and adhering to the posterior cornea. A patient with polycythemia described by Lousea et al. had a one-and-a-half syndrome from an infarction of the pons.[5]

In the study performed by Jabaily et al., visual disturbances occurred in 6 of 33 patients and included scintillating scotomas, episodic dimming of vision, and amaurosis fugax . Murphy et al. reported that 10 of 37 patients with essential thrombocythemia had visual phenomena as part of their disease. Among 33 patients reported by Michiels et al., 10 had visual symptoms: transient monocular blindness in 3, and blurred vision in 10 patients.[6]

ANEMIAS

Definition:

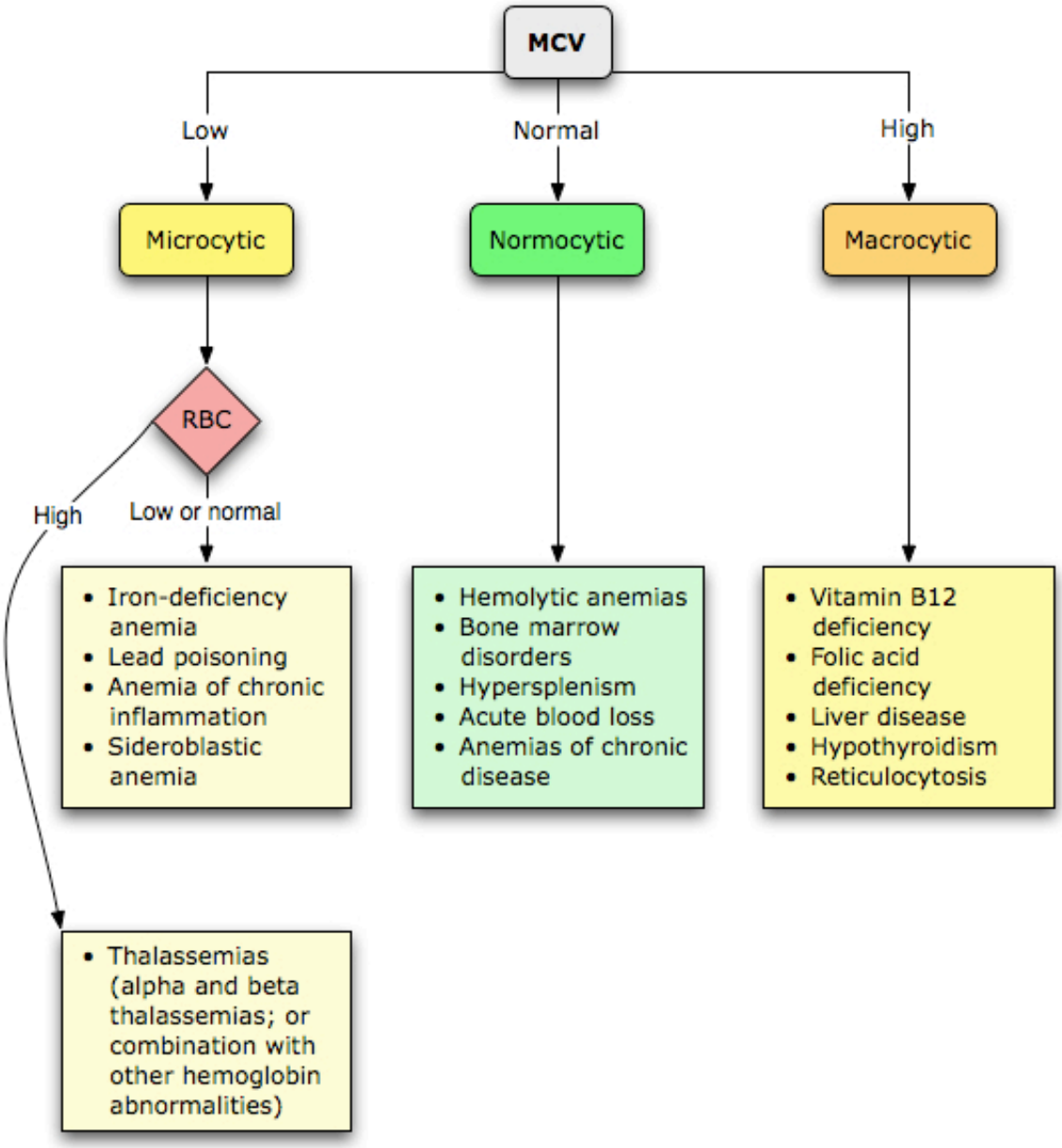
Anemia is defined as a low Hb level (< 13 g Hb/dL in men and < 12 g Hb/dL in women), decreased number of circulating RBC (< 4.4 millions/cumm in men and < 3.8 millions/cumm in women), or both, resulting in diminished oxygen-carrying capacity of the blood.

General manifestations are due to:

i) Decreased Hb concentration (pallor of skin, conjunctiva and nail beds),

ii) Tissue hypoxia due to deficient oxygen transport (weakness, easy fatigability, exertional dyspnea), and

iii) Recruitment of compensatory mechanisms (cardio-circulatory, biochemical and medullar) aimed at increasing cardiac output and oxygen delivery to the tissues.


MCV
Low
Normal
High
Microcytic
Normocytic
Macrocytic
RBC
High
Low or normal
• Iron-deficiency anemia
• Lead poisoning
• Anemia of chronic inflammation
• Sideroblastic anemia
• Hemolytic anemias
• Bone marrow disorders
• Hypersplenism
• Acute blood loss
• Anemias of chronic disease
• Vitamin B12 deficiency
• Folic acid deficiency
• Liver disease
• Hypothyroidism
• Reticulocytosis
• Thalassemias (alpha and beta thalassemias; or combination with other hemoglobin abnormalities)

Classification:

1) Morphologic classification (according Hb, Ht red cell indices and the peripheral blood smear)subdivides anemias into:

1. Microcytic hypochromic anemias
2. Macrocytic normochromic anemias
3. Normocytic normochromic anemias

2) Functional classification (according the reticulocyte count) comprises:

1. Regenerative anemias (> 3%)
2. Aregenerative anemais (< 3%)

3) Etiopathogenic classification: Anemias may result from:

4) Decreased red cell production (decreased erythropoiesis)

5) Increased red cell destruction (increased hemolysis)

6) Anemias due to decreased erythropoiesis

7) Decreased erythropoisis

8) Nutrional deficiency:

1. Deficiencies in hemoglobin synthesis:
    a. Iron deficiency anemia
    b. Sideroblastic anemia
2. Deficiencies in DNA synthesis:
    a. Vit. B12 deficiency
    b. Folate deficiency

9) Bone marrow failure:

   a) Pluripotential stem cell failure:

      i) Aplastic anemia

      ii) Anemia of leukemia and of myelodysplastic syndromes

   b) Erythroid progenitor cell failure:

      i) Anemia from chronic disease/inflammation

      ii) Anemia from chronic kidney disease

1. IRON DEFICIENCY ANEMIA

Definition:

The most common form of anemia worldwide characterized by microcytosis, hypochromia ,decreased iron stores(low ferritin) and low serum iron.

Iron metabolism:

Iron balance depends on adequate intake, absorption, recycling and loss. The total body iron content is about 3.5 g in men and 2.5 g in women and is divided into functional and storage compartments. Functional iron (80%) is found in hemoglobin, myoglobin and iron-containing enzymes whereas the storage compartment is represented by ferritin (rapid available iron, a combination of iron and apoferritin), and hemosiderin. Hepatocytes are the main site of ferritin storage and minute quantities are present in plasma in equilibrium with the intracellular ferritin.

Hemosiderin is mainly stored in the macrophage-monocyte system as aggregates or crystals of ferritin with the apoferritin partially removed.

2. VITAMIN B12 AND FOLIC ACID DEFICIENCY ANEMIAS

Definition:

Megaloblastic, macrocytic, normochromic anemias that share as common feature an impairment of DNA synthesis.

General features:

Both B12 and folate are cofactors in the synthesis of thymidine, one of the four bases in DNA. The inadequate DNA synthesis results in defective nuclear maturation and a delay in cell division (cell size increases) whereas cytoplasmic maturation and

hemoglobin accumulation proceed normally,leading to nuclear-to-cytoplasmic asynchrony.

Bone marrow:

Megaloblastic changes are detected at all stages of erythropoiesis (promegaloblasts, megaloblasts) with a decreased production of mature RBC and release into the peripheral blood, causing anemia. The megaloblasts may undergo autohemolysis in the marrow or are destroyed by phagocytic cells in the marrow (ineffective erythropoiesis). Megakaryocytes are abnormally large too.

Peripheral blood:

The presence of abnormally large red cells (high MCV) -macrocytes and macro-ovalocytes is highly characteristic. Large and hypersegmented neutrophils may be seen secondary to the delay in mitotic division. The impairment of DNA synthesis is systemic, and affects other rapidly dividing cells in the body, e.g. gastrointestinal epithelial cells. Since the megaloblastic features are indistinguishable morphologically in folate and B12 deficiencies, diagnosis is established by laboratory tests (serum B12 and folate levels).

3. APLASTIC ANEMIA

Definition:

A normochromic normocytic anemia due to a defect of the pluripotent stem cells responsible for primary hematopoietic failure with:

- Marked Bone Marrow Hypocellularity & fatty replacement of bone marrow – Pancytopenia (anemia,neutropenia,thrombocytopenia) in the peripheral blood

Etiology:

a) In 2/3 of the cases-idiopathic Aplastic anemia (no detectable initiating factor).

b) The rest of the cases occur secondary to:

   i) Chemical toxins (benzene, chlorinated hydrocarbons)

   ii) Drugs: Alkylating agents and Antimetabolites used in cancer therapy (dose related effect) and chloramphenicol, phenylbutazone (idiosyncratic mechanism)

   iii) Viral infections(Hepatitis, AIDS, Mononucleosis)

   iv) Autoimmune disorders (SLE, Hashimoto Thyroiditis)

Pathogenesis:

Two major pathogenetic theories exist:

1. An extrinsic immune-mediated suppression of marrow precursors triggered by exposure to chemicals, infectious agents, etc. with the production of cytokines (TNF and IFN) that are directly responsible for the suppression of haematopoiesis.

2. An intrinsic abnormality of stem cells (reduced proliferative capacity) Clinical problems result from anemia (weakness, fatigue), leukopenia (infections) and decreased platelets (bleeding). Bone marrow transplantation has been successful, especially in patients less than 40 years old.

4.ANEMIA FROM CHRONIC DISEASE/INFLAMMATION

Definition:

characterized by:

- low serum iron level
- increased ferritin level(reflecting the excessive iron stores).

Etiology:

1) Chronic infections (AIDS, osteomyelitis)
2) Chronic inflammations (Inflammatory bowel disease)
3) Autoimmune disorders (Lupus Erythematosus, Rheumatoid Arthritis)
4) Cancer (Hodgkin's disease)

Pathogenesis:

Microorganisms, injured tissues, autoimmune dysregulation and tumor cells lead to T–cell activation and production of cytokines (IL-1, IL-6, TNF-Į, IFN) that are responsible for: increased production of hepcidin by the liver(IL-6) which inhibits iron release from hepatocytes, enterocytes and macrophages .

- macrophage sequestration of iron with decreased serum iron level & availability for Erythropoiesis
- macrophage activation with increased splenic destruction of red cells (hypersplenism- RBC lifespan is decreased by 20 to 30%)
- reduced production of erythropoietin(EPO) and/or resistance to EPO
- resulting in decreased Erythropoiesis

5. HEMOLYTIC ANEMIAS

Hemolytic anemias are characterized by shortened red cell survival. Increased Erythropoietin production results in increased red cell production with a Reticulocytosis to compensate for the anemia.Red cell destruction can occur within the spleen macrophages (Extravascular hemolysis) or within circulation (intravascular hemolysis). Another feature is the retention of Hb degradation products in the body increased serum levels of indirect bilirubin > 2.5 mg/dl causing jaundice.

Extravascular hemolysis: Destruction of red cells in the mononuclear phagocytic system(spleen, liver) – the normal place of physiologic hemolysis of senescent erythrocytes.

Damaged or abnormal RBC are removed in spleen, where Hemoglobin is broken down Intracellularly. Free Hemoglobin is not released directly into the blood and urine, but hemoglobin breakdown products are increased (hyperbilirubinemia) and jaundice may result.

Spleen and liver may become enlarged since these are sites of removal of RBC from the circulation. Chronically elevated levels of bilirubin can promote formation of gallstones. Intravascular hemolysis leading to destruction of RBC within the circulation.

6. THALASSEMIA

Definition:

Is an inherited defect (Autosomal dominant) that results in diminished or absent synthesis of either the alpha or beta globin chains of hemoglobin. The type of Thalassemia is named for the globin chain produced in reduced amounts. Decreased

globin production leads to decreased hemoglobin production and anemia, as major manifestation. In addition, precipitation of the relative excess of the other globin chain within RBC is responsible for membrane damage and premature destruction of RBC precursors in the marrow (ineffective erythropoiesis) and spleen (extravascular hemolysis).

Clinical manifestations vary from severe transfusion-dependent anemia and iron overload to mild anemia. In almost all cases there is a moderate to marked microcytosis with target cells and basophilic stippling of the red cells present on the blood smear.

POLYCYTHEMIA:

The opposite of anemia is polycythemia, which is characterized by: An increase in the number of circulating red cells-an increase of the haematocrit (Ht) (over 45% in females, over 48% in males).

The pathophysiological consequences of the increasing haematocrit are:

- an increase of blood viscosity, which can lead to an increased risk of thrombosis and a decrease in the tissues' blood and oxygen supply, thus leading to hypoxia and an overload of the heart function.

The increased medullary activity will be accompanied by an increased cellular destruction, which can lead to a high level of uric acid (risk for developing gout).

Polycythemia is divided into:

- Relative polycythemia (erythrocytosis) (the red cell mass is normal, but the plasma volume is reduced)
- Absolute polycythemia (erythrocytosis) (a true increase in red-cell mass).

WHITE BLOOD CELLS

1) NON – MALIGNANT disorders of white blood cells
    a) Disorders due to a abnormal number of white blood cells
        1. Leucocytosis
        2. Leucopenia
    b) Disorders due to abnormal function of white blood cells
2) MALIGNANT disorders of white blood cells
    a) WHO classification of white cells neoplasm
    b) Leukemia
    c) Lymphomas
    d) Plasma cell neoplasm

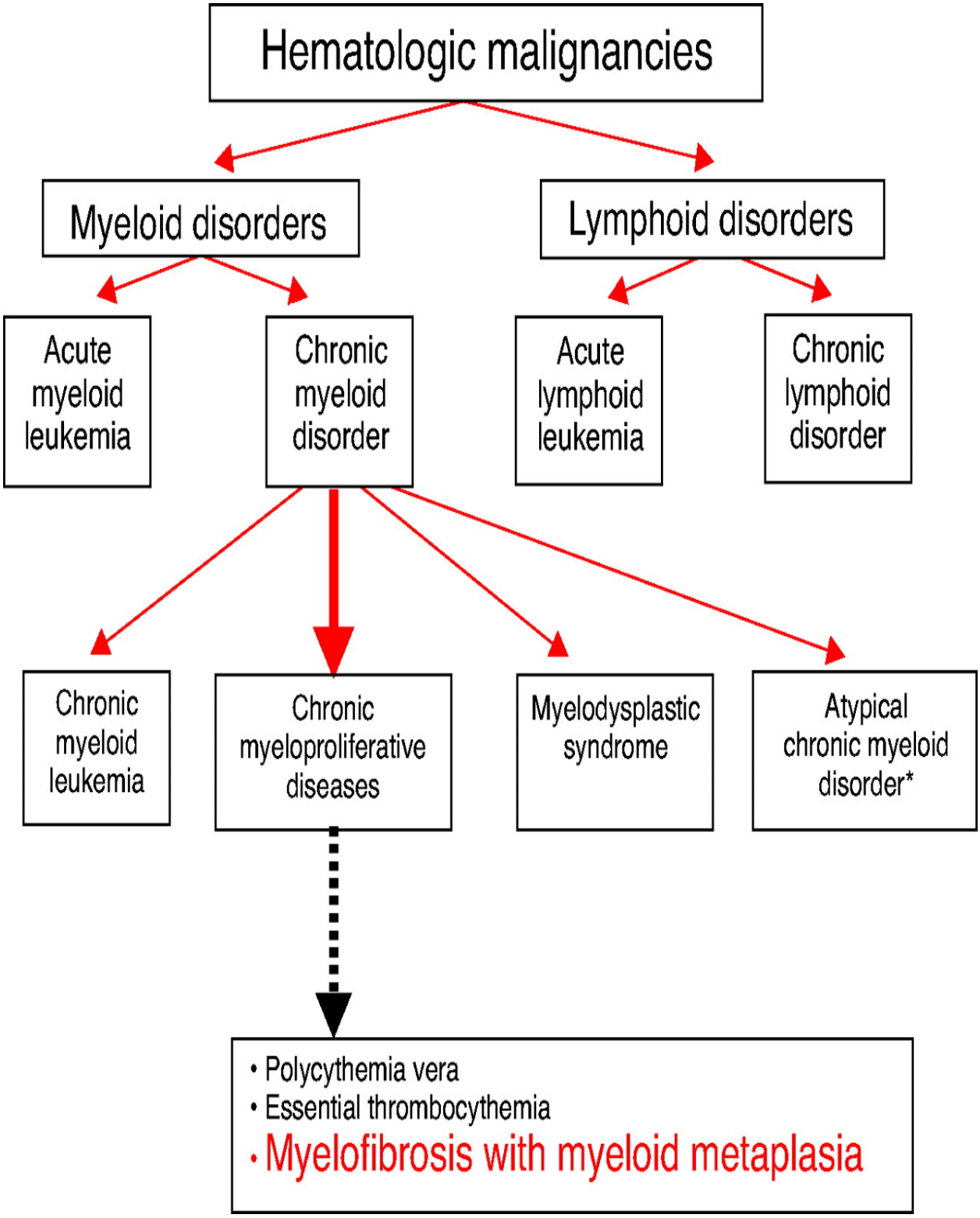
NON – MALIGNANT DISORDERS OF WHITE BLOOD CELLS

A. Disorders due to abnormal number of white blood cells:

1. **Leucocytosis**: increase of the number of white cells > 10,000/cumm
2. **Leucopenia**: decrease of the number of white cells < 4,000/mm

MALIGNANT DISORDERS OF WHITE BLOOD CELLS

Hematological malignancies have been classically divided by whether the malignancy is mainly located in the blood (leukemia) or in the lymph nodes (lymphomas).


Hematologic malignancies
Myeloid disorders
Lymphoid disorders
Acute myeloid leukemia
Chronic myeloid disorder
Acute lymphoid leukemia
Chronic lymphoid disorder
Chronic myeloid leukemia
Chronic myeloproliferative diseases
Myelodysplastic syndrome
Atypical chronic myeloid disorder*
• Polycythemia vera
• Essential thrombocythemia
• Myelofibrosis with myeloid metaplasia

LEUKEMIA:

are primary neoplasm of the bone marrow (BM) With characteristic spilling over of the malignant cells into peripheral circulation.

LYMPHOMAS:

are primary neoplasm of lymph nodes/lymphoid tissues that usually do not involve peripheral spill over of malignant cells.

LEUKEMIAS

Definition:

malignant disorders resulting from an abnormal proliferation in the bone marrow, with invasion of the blood stream.

Classification:

I. According to the evolution:

1. Acute leukaemia:

in which accumulation of immature cells (blasts) suppresses normal hematopoiesis.

2. Chronic leukaemia:

characterized by an abnormal proliferation of the mature cells having better prognosis and longer evolution.

II. According to the abnormal cell type:

1. Myeloid Leukemia (Acute, Chronic)

2. Lymphoid (lymphocytic) Leukemia (Acute, Chronic)

Consequences:

in blood cell number and function

a) Infections : Most common cause of death

Due to severe infections (neutropenia, impairment of phagocytic function and lymphocyte function)

b) Haemorrhage :Due to thrombocytopenia or liver disease

c) Anemia : Due to replacement of RBC precursors by cancer cells

Prognosis of leukemia:

1.Severity of anemia reflects severity of disease

2. Invasion of vital organs (enlargement of spleen, liver, brain, lung, and lymph nodes)

ACUTE LEUKEMIA

Definition: acute leukemia develop as a consequence of an abnormal proliferation of blasts (immature cells) that leads to hematopoietic suppression.

Classification:

1. Acute Myeloid leukemia (AML)

2. Acute Lymphoid leukemia(ALL)

CHRONIC LEUKEMIA

Definition: chronic leukemia develop as a consequence of increased proliferation and accumulation of differentiated, mature leukemia cells.

Classification:

1. Chronic myeloid leukemia (CML)

2. Chronic lymphoid leukemia (CLL)

LYMPHOMAS

Definition:

malignant disorders caused by abnormal proliferation of the cells that reside in the lymphoid tissues. Morphologically, these neoplasms are solid tumors of the lymphoid tissue that do not lead to peripheral blood invasion. However, if such an invasion were to take place, it will be described as a leukemia phase of the lymphoma.

Classification:

- Hodgkin's lymphoma
- Non – Hodgkin's lymphoma

Both diseases invade the lymphoid tissues, but the difference between them resides in the biological, clinical and prognosis features.

OCULAR FEATURES IN DISORDERS OF RBC:

RBC disorders that ophthalmologists frequently encounter include anemias and sickle cell disease.

• **Anemia**:

Anemia is a common condition occurring when the level of healthy RBCs/erythrocytes or hemoglobin, is subnormal. Causes include increased blood loss, inadequate production of RBCs by the bone marrow (aplastic anemia) and destruction of RBCs (hemolytic anemia). Additional causes include iron, vitamin B_{12} (pernicious anemia) or folic acid deficiencies, which are related to poor nutrition or absorption defects in the gastrointestinal tract. General symptoms include pallor of the skin or nail beds, weakness, headaches, shortness of breath, gastrointestinal disturbances, fever, and numbness or coldness of extremities.

Diagnostic tests:

CBC-The key components of the complete blood count (CBC) indicating anemia are decreased RBC count, low hemoglobin (Hgb) and reduced hematocrit (HCT). MCV-Mean corpuscular volume, a measurement of average size of the red blood cells, helps to identify the type of anemia. The normal range of MCV is from 80fL to 100fL. The anemia is classified as microcytic if MCV falls below 80fL; if above 100fL, the anemia is classified as macrocytic. A major cause of microcytic anemia is iron deficiency and macrocytic anemia is folic acid or vitamin B_{12} deficiency.

Iron is a major component of hemoglobin, essential for its proper function in transporting oxygen. Additional testing such as serum ferritin (a major storage form of iron) test or total iron binding capacity (TIBC) test (which is a measure of transferrin, a protein that helps transport iron in the blood) are needed to make a diagnosis of iron deficiency anemia.

Other investigations- Folic acid or vitamin B_{12} serum levels or a bone marrow biopsy to rule out a plastic anaemia.

Many systemic diseases such as cancer, inflammatory diseases and pregnancy may present with anaemia. So appropriate investigations may be necessary to identify the underlying cause of the anemia.

OCULAR FEATURES IN ANEMIA:

Ocular changes in anemia include conjunctival pallor and hemorrhages. Anemic retinopathy and other retinal changes are well established complications of anemia. Common retinal findings include intraretinal hemorrhages, Roth's spot hemorrhages, cotton-wool spots, retinal exudates, venous dilation and optic nerve pallor. The exact pathophysiology of the retinopathy is not clearly understood, but seems to be related to retinal hypoxia. These changes are generally seen in severe anemia or when thrombocytopenia is present.

The normal color of the ocular fundus is derived from retinal pigment epithelium (RPE), choroidal melanocytes, and blood in the retinal and choroidal vasculature. The

retina is normally transparent. In patients with severe anemia, the fundus may appear pale and the retinal vessels may be less red than normal.

Anaemia is the commonest haematological disorder presenting with variety of ocular manifestations. It can affect every part of the eye and adnexa but predominant features are conjunctival pallor and retinal haemorrhages. Other retinal manifestations include venous and arteriolar tortuosity, cotton wool spots, macular star and papilledema. Their increased incidence is correlated with severity of anaemia. The substrate for retinal metabolism is reduced in anaemia and makes it prone for hypoxic damage.

Anemic retinopathy has been associated with diseases of the red blood cell elements or as a secondary manifestation of other systemic diseases, and it should be noted that many of the systemic diseases involved may be associated with similar retinal findings and are not exclusive of anemia per se. Hence, it has been appropriately suggested that since anemic retinopathy is almost always reversible with correction of the anemia, one should be reluctant to ascribe retinal changes entirely to concomitant systemic disease until restoration of normal haemoglobin levels and fundoscopic re evaluation.

In optic disc edema, nerve fiber swelling in the optic disc and peripapillary retina is present and often associated with flame-shaped hemorrhages, whitish punctate lesions (secondary to obstructed axoplasmic flow), and peripapillary CWSs. On ophthalmoscopy, the optic disc and peripapillary retina appear elevated and the margins of the optic disc are blurred. Optic disc edema is usually bilateral and may be due to elevated intracranial

pressure (i.e., papilledema) secondary to hemorrhage or a mass effect associated with blood dyscrasias (i.e., meningeal infiltration, granulocytic sarcoma). The disc edema may also be secondary to serum (blood) hyper viscosity and may resemble that seen in CRVO. Less commonly, direct infiltration of the optic nerve or optic disc may cause marked optic disc edema.

RETINAL HEMORRHAGES:

The configurations of retinal hemorrhages depend on where they are located within the retina. In blood dyscrasias, flame-shaped and dot-blot hemorrhages are the most commonly and frequently encountered. Nerve fibre layer houses the flame-shaped hemorrhages whereas the inner nuclear and outer plexiform layers house the dot-blot hemorrhages. Seen beneath the internal limiting membrane of the retina are large boat or blot-shaped hemorrhages i.e., sub-ILM hemorrhage which are large superficial retinal hemorrhages, which extend into the vitreous cavity after breaking through the internal limiting membrane. Retina of patients with blood dyscrasia contain white-centred hemorrhages and red-centred infiltrates. Leukemic embolus or more commonly platelet-fibrin thrombus may be the reason behind the white centre. Red centred infiltrates are of blood which may be seen in association with leukemic retinal infiltrate or cotton wool spot.

MICRO-ANEURYSMS:

Micro-aneurysms are defects which are seen as outpouchings of the retinal capillary wall. On ophthalmoscopic examination, they appear as small reddish spots in

the retina. In diabetic retinopathy, they are visualized in the posterior aspect of the fundus. Microaneurysms are also seen in certain other conditions like leukemia and plasma cell dsycrasia. In blood dyscrasias these lesions are visualized in the periphery of the retina whereas in diabetic retinopathy they are seen in the posterior retina.

Duke and co-workers in his study which involves trypsin digestion of flat mounts of the retina, found that relative preservation of pericytes in patients with chronic leukemia as compared with the marked loss of pericytes in diabetic retinopathy. The lesion's globular shape, its location on the capillary's venous side predominantly and intraluminal and intramural periodic acid Schiff positive deposits are the common pathological features between micro aneurysms of Blood dyscrasias and diabetes.

Factors like increased venous pressure (CRVO), increased blood viscosity with secondary increase in venous pressure (hyperviscosity syndrome associated with plasma cell dyscrasias) and anoxia (anemia) play a vital role in the formation of micro-aneurysms in cases of blood dyscrasias.

RETINAL EDEMA:

Hyper permeable or leaky retinal capillaries is also a causative factor of focal or generalized retinal edema, in addition to hard exudates formation. Normally the retina is transparent, however there is greying or mild pacification of the retina on ophthalmoscopic examinationin retinal edema. In long-standing cases of retinal edema, cystic degeneration of the retina may occur. Cystoid macular edema is when the retinal edema which is localized to the macular region. From a histological point of view, cysts in CME consist of eosinophilic proteinaceous material which is located in the outer

plexiform layer and in the inner nuclear layer of retina, to a lesser extent. Observations of lipid-laden macrophagesin the region of cystoid macular edema have been made occasionally. In hyperviscosity syndromes induced by blood dyscrasias, retinal edema may be seen, as with hard exudates. Blood dyscrasias induced CME show response to specific therapy for CME (i.e. Acetazolamide) and with treatment of the underlying disease like bone marrow transplantation in CME, CME resolves completely.

COTTON WOOL SPOTS:

Otherwise called soft exudates, are micro-infarctions present in the retina's nerve fibre layer. When focal retinal ischemia occurs due to pre-capillary arteriolar occlusion, normal axoplasmic flow is blocked. They are whitish superficial lesions on the retina with feathery borders in association with small retinal hemorrhages. These lesions resolve and fade, developing an area of depression in the retina which is secondary to inner retinal ischemic atrophy. Microscopically, they are fusiform thickenings of the nerve fibre layer with globular cystoids bodies [swollen ganglion cell axons with cellular organelles like mitochondria, endoplasmic reticulum and neurofilaments which are degenerated]. In patients afflicted with blood dyscrasias induced retinopathy, CWSs are seen. In one report, in the absence of diabetes and hypertension, if a single CWS is seen in each eye, diagnosis of MM is made. In a prospective study of 54 newly diagnosed patients with acute leukemia, Abu El-Asrar and co-workers[(19)] reported that patients with CWSs had significantly lower mean and median survival times than those patients without CWSs. Poor prognostic sign for a patient's survival in acute leukemia is the presence of CWSs.

Severe anemia is a prominent risk factor in the development of CWSs in patients afflicted with blood dyscrasias. Holt and Gordon-Smith[3] observed CWSs in 14 patients with severe anemia with a mean hemoglobin concentration of 5.6 g/100 ml.In contrast, Guyer and co-workers[4]found no statistically significant association between the presence of CWSs and hematologic parameters (including the hematocrit) in their prospective series. CWSs occur due to pre-capillary arteriolar occlusion by leukemic cells or by platelet-fibrin thrombi.

VASCULAR OCCLUSIONS:

Visual disturbances in patients with essential thrombocythemia are related to thrombotic, hemorrhagic, and possibly vasomotor phenomena.The ocular abnormalities seen in patients with polycythemiavera are similar to those seen in patients with other hyper viscosity syndromes. Their severity is related to that of the polycythemia and its duration. Many patients develop engorgement of the conjunctival and retinal vessels. The associated ischemic disorders of the eye may become manifest as dilated, tortuous vessels, retinal hemorrhages, central retinal artery occlusion (CRAO), central retinal vein occlusion (CRVO), and anterior ischemic optic neuropathy (AION). CRVO may be bilateral.

As mentioned above, papilledema may result from the effects of thrombosis of the cerebral venous sinuses. Optic disc swelling may also result from local vascular changes related to hyper viscosity.

It is important to rule out other ocular and concomitant systemic diseases, as the ocular changes of anaemia are non-specific and may closely resemble other conditions.

The ocular complications are usually reversible with correction of the anemia. Pallor of the optic nerve requires imaging studies. These patients should be monitored frequently with three to six month follow-up evaluations.

SICKLE CELL DISEASE:

It is an inherited autosomal recessive disorder due to abnormal hemoglobin resulting in a crescent-like, or sickle-shaped RBCs usually in association with decreased oxygen. Normal blood flows is prevented by the sickled RBCs, leading to increased blood viscosity and decrease the RBCs' ability to carry oxygen, which results in chronic haemolysis and vaso-occlusive events that produces tissue and organ damage.

The four most common hemoglobin variants include: sickle cell anemia (SS), associated more with systemic complications; sickle cell thalassemia (S-thal) and sickle cell C disease (SC), more commonly associated with severe ocular complications; and sickle cell trait (AS), occuring when one normal hemoglobin gene and one sickle hemoglobin gene are inherited.

The diagnosis begins with observation of ocular changes, which result from the sickling of RBCs within small vessels leading to micro vascular occlusion. The resulting features include ischemia, hypoxia, infarction, "sea-fan" neovascularisation and fibrovascularization.

POLYCYTHEMIA:

Polycythemia is a sustained increase in erythrocyte count, blood haemoglobin Concentration, and hematocrit. Polycythemia may be secondary to a myriad of conditions causing chronic hypoxemia or elevated erythropoietin production. Polycythemia vera is a myeloproliferative disorder of middle or later life often associated with leukocytosis and thrombocytosis.

Late in the course of polycythemia vera, there is a transition to a disease state that involves myeloid metaplasia with myelofibrosis. This is associated with extramed ullary hematopoiesis (blood cell production outside the bone marrow). This process rarely occurs outside the cranium. However, there have been two cases of extramedullary hemato-poiesis invading the optic nerve sheath. On computed tomography scanning, this appears as a well-demarcated retro bulbar mass along the optic nerve.

Haematological diseases, such as anaemia encompass a wide spectrum of disorders ranging from benign to malignant conditions that can present with ocular involvement. Mostly the ocular manifestations may be the initial indication of an underlying haematological disorder, which often requires a laboratory work-up to clinch a final diagnosis.

THROMBOCYTOPENIA:

Idiopathic thrombocytopenia is a disease primarily caused due to increased platelet destruction with formation of specific antibodies against platelet membrane glycoprotein. ITP often follows an in infection in the acute form and shows spontaneous resolution

while in chronic ITP, it persists for more than 6 months. Thrombocytopenias are commonly related to intake of specific drugs such as Quinolones, Sulphonamides.

LEUKEMIA

Leukemia are neoplasm of the hematopoietic system. Leukemic cells show a poor responsiveness to normal regulatory mechanisms, have a diminished capacity for normal cell differentiation, and can have malignant transformation occurring at any stage of haematopoiesis. Abnormalities may affect the lymphopoietic or myelopoietic arms of hematopoiesis, resulting in a myelogenous or lymphocytic leukemia, respectively. Leukemia can occur in a rapid and aggressive form (acute) or an indolent form (chronic). These combinations account for the four broad categories of leukemia:

(1) Acute Myelogenous Leukemia (AML),

(2) Acute Lymphocytic Leukemia (ALL),

(3) Chronic Lymphocytic Leukemia (CLL), And

(4) Chronic Myelogenous Leukemia (CML).

Although all types of leukemias can affect patients at almost any age, typically AML affects males older than 50 years, ALL tends to affect children younger than 15 years of age, CLL affects patients older than 50 years of age, and CML affects patients in the 5th decade with a slight male predominance [6]

Almost every structure in the orbit, the globe as well as adnexa may be involved in these conditions. Lymphomas of the eye are mostly of the B cell lineage.

PLASMA CELL DYSCRASIAS/ PARAPROTEINEMIAS:

Plasma cell dyscrasias are characterized by malignant proliferation of B cells with subsequent overproduction of immunoglobulin (antibodies).

They are classified into three major types:

(1) Multiple myeloma with overproduction of either IgG, IgA,IgD or IgE;

(2) macroglobulinemia with overproduction of IgM; and

(3) light- and heavy-chain diseases.

OCULAR CHANGES IN MALIGNANT DISEASES OF BLOOD

The ocular changes in leukemia are predominantly divided into anterior segment manifestations and posterior segment manifestations.Anemia, Thrombocytopenia, elevated white blood cell count and blood or serum hyperviscosity are the contributing factors which promote the development of retinal hemorrhages in patients with blood dyscrasias.[9] Rubenstein and co-workers in a study conducted in a group of 67 patients found that retinal hemorrhages presented more commonly in patients with both anemia and thrombocytopenia than when either is present alone. It was postulated by the same authors that in an anemic patient, ocular bleeding could be attributed to thrombocytopenia.

Holt and Gordon-Smith in their study conducted on 152 patients with blood diseases, [10] found that retinal hemorrhages were seen more commonly in leukemic patients with very severe anemia and thrombocytopenia with higher percentage of circulating blast cells. The findings of the prospective study conducted by Guyer and colleagues in a group of 117 patients with acute leukemia further supported that

thrombocytopenia plays a significant role in the pathogenesis of retinal hemorrhages. [11]However Jackson and co-workers in their study on 63 newly diagnosed acute leukemia patients, saw no allegiance between intraretinal hemorrhages and hemoglobin level or platelet count. But they also found out that higher median white blood cell count was seen in patients with intraretinal hemorrhages than in patients without intraretinal hemorrhages providing the conclusion that in the pathogenesis of retinopathy in acute leukemia, high white blood cell count is as important as anemia and thrombocytopenia.[12]

Perivascular sheathing and retinal vasculitis (leakage from retinal vessels on fluorescein angiography) have been prominent ocular findings in patients with certain blood dyscrasias, including human T-lymphotropic virus 1 (HTLV-1)-associated adult T-cell leukemia/lymphoma, cryoglobulinemia, hairy cell leukemia, and, rarely, MM.Kim and coworkers described a patient with relapsing acute lymphoblastic leukemia who presented with a retinal vasculopathy resembling frosted branch angiitis and an infiltrative optic neuropathy that resolved with local radiation and intrathecal chemotherapy.[13]

ANTERIOR SEGMENT MANIFESTATIONS:

Sclera:

Infiltration of the sclera or episclera by leukemic cells is usually found at autopsy and rarely produces any clinical symptoms or signs. The cells are most often present in the episclera, with a perivascular distribution. [12]

Conjunctiva:

Involvement of the conjunctiva most often occurs in patients with lymphocytic leukemia, but it also occurs in other types. Cellular invasion ccurs at all levels of the substantia propria. It may be diffuse or patchy, although it tends to concentrate around blood vessels. In some cases the involvement consists of visible nodules with surrounding injection resembling areas of focal episcleritis, whereas in others there is only slight swelling of the conjunctiva, and in still others there is diffuse and substantial swelling leading to limitation of eye movements.[13] As with other ocular manifestations of leukemia, conjunctival involvement may occur at any time during the course of the disease and may even be its first sign. The most frequent ocular findings were seen in conjunctiva (33.4%) among leukemics in a study in Poland [8]. Multiple myeloma is one of the causes of a salmon patch conjunctival lesion.

Cornea:

As cornea is avascular, the invasion of cornea by leukemic cells is not expected. But leukemia may cause formation of a sterile ring like ulcer associated with iritis and formation of pannus. This ring lesion also called an immune ring, may be observed even

prior to the diagnosis of leukemia and hence a patient presenting with a corneal ring ulcer should be evaluated thoroughly for systemic illnesses, including leukemias. [14]

Multiple myeloma frequently presents with a complication of corneal precipitates that have been reported for over 70 years. These crystalline corneal precipitates have been reported to be deposits of immunoglobulins, primarily IgG. The source of these immunoglobulins have been attributed to high immunoglobulin levels in tears or aqueous humor leading to corneal crystals, the immunoglobulins which reach the cornea through limbal vessels as well as from the keratocytes supplying the precipitated immunoglobulins. These were observed as 6-11nm sized numerous hyperreflective globules at the level of the corneal epithelium and anterior stroma and obscured normal architectural detail of the cornea in cases of multiple myeloma. The development of the crystals can precede systemic evidence of multiple myeloma by several years. [13]

Anterior chamber:

Anterior chamber leukemic cells and flare, pseudohypopyon and hyphema can occur in the anterior chamber. A shallow anterior chamber can be present due to iris swelling secondary to leukemic infiltrate.Anterior chamber infiltration–simulating hypopyon (pseudohypopyon) can occur in multiple myeloma. [16]A pseudohypopyon is characterized by its persistence and irregular contour, which suggest clumping of neoplastic cellular material rather than the layering of neutrophils, as in anterior uveitis. Bronstein reported plasma cells floating free in the anterior chamber and adhering to the posterior cornea .[11]

Uvea:

Cysts of the ciliary body represent the most common ocular manifestations in myeloma patients. Infiltration of the iris has also been reported, simulating a non granulomatous uveitis. Metastatic carcinomas of the iris, which typically appear as solid, amelanotic masses, occasionally are shed cells that form a hypopyon in the anterior chamber[(14)].

Infiltration of the anterior segment by leukemic cells occurs rarely in patients. It usually occurs in patients with acute leukemia but may also occur in patients with chronic leukemia. In some patients, usually children, a spontaneous hypopyon-hyphema is the first evidence of the disease, whereas in other patients with known leukemia, involvement of the iris and anterior segment is the first or only evidence of relapse of the disease. [(12)]The condition is characterized by conjunctival injection, symptoms of acute iridocyclitis, and a hypopyon that may be tinged with blood.

There may be elevated intraocular pressure. Infiltration of the iris may be diffuse or nodular. Diffuse infiltration discolors the iris, which appears to be covered by a whitish-gray film, and it produces hyperchromia or hypochromia iridis when the process is unilateral. If there is nodular infiltration, the nodules are seen over the iris. The diagnosis of anterior segment involvement by leukemia can be confirmed by paracentesis with cytologic examination of the aqueous humor. The condition can be treated effectively with low-dose irradiation to the anterior portion of the globe.[(17)]

Neuro-ophthal manifestations:

Third nerve palsy, lower motor neuron facial nerve palsy and 6th nerve palsy have been reported in association with leukemias.CLL can present with acute optic neuropathy associated with cerebrospinal fluid evidence of meningeal spread of malignant cells .Visual loss in myeloma is usually caused by compression or infiltration of the optic nerves by tumor. The mechanism of optic neuropathy in this case is probably related to infiltration of the optic nerve meninges by malignant plasma cells and impaired vascular supply caused by aggregated intraluminal plasma cells and monoclonal hypergammaglobulinemia. [18]

In one study, neuro-ophthalmic symptoms resulting in diplopia or visual disturbances were reported. Neurological complications of leukemia are caused by a variety of different processes.[15]

1. Neurologic injury may be caused by leukemic invasion of the leptomeninges, parenchyma, spinal cord, nerve roots, and peripheral nerves.

2. Leukemia may cause cerebrovascular disorders, both hemorrhagic and ischemic, by obstructing intracranial vessels.

3.Neurologic sequelae may result from the various forms of treatment of the disease.

4.Paraneoplastic.

In most cases, however, leukemic involvement of the CNS occurs from hematogenous spread or by direct invasion from adjacent affected bone marrow.[19]

CNS leukemia is diagnosed by cerebrospinal fluid (CSF) analysis, requiring a minimum of five white blood cells per microliter and the presence of leukemic blast cells by cytospin technique. Since the advent of successful therapy of leukemia, the meninges have become the major site of leukemic relapse.

With the advent of intrathecal chemotherapy and cranial irradiation as routine CNS prophylaxis, the incidence of meningeal leukemia has declined to approximately 10%. For those who suffer meningeal involvement following radiation therapy, however, prognosis is poor. Meningeal involvement occurs more commonly in acute lymphoblastic leukemia than in acute myeloblastic leukemia and is rare in the chronic lymphocytic leukemias .[21]

Meningeal leukemia may produce a variety of symptoms from single as well as multiple cranial neuropathies and may also cause increased ICP. Affected patients may thus develop headache, meningismus, nausea, vomiting, papilledema, increasing lethargy, and focal neurologic signs, including diplopia from ocular motor nerve paresis.

In most cases, leptomeningeal and parenchymal infiltration occurs at a relatively late stage of the disease after the diagnosis is established, but this is not always the case. In a series of 30 children with neurological presentations of malignancy, one-third had acute leukemia. Papilledema and ocular motor neuropathies may be presenting manifestations of acute lymphocytic leukemia. Leukemic involvement of the brain parenchyma is usually an extension of meningeal infiltration, but rare autopsy results document isolated leukemic parenchymal collections. These may be the result of a mechanism other than invasion from the meninges or from treatment that suppresses

meningeal leukemic cells but spares those deep within the parenchyma. Parenchymal involvement is usually perivascular.

Chloromas are usually single, but they may be multiple. They may arise in various locations in the CNS parenchyma and dura. They are isointense to white matter on magnetic resonance (MR) T1- and T2-weighted images and are isointense to hypointense on computed tomographic (CT) imaging, enhancing with contrast.

Leptomeningeal infiltration can lead to infiltration of the intracranial portions of the optic nerves and optic chiasm. In most patients, visual loss may be slow and progressive, responding to radiation therapy, or extremely rapid.

Cerebrovascular disorders may produce neurological dysfunction in patients with leukemia. The majority is hemorrhagic, caused by invasion of blood vessel walls by leukemic cells, thrombocytopenia, sepsis, and disseminated coagulopathy. Blast crisis, extreme leukocytosis, and thrombocytopenia are predisposing factors.

Intracranial hemorrhage contributes to mortality in 10 to 21% of leukemic patients. Cerebral ischemia is less common than hemorrhage and may result from arterial or venous obstruction. In leukemic patients, cerebral venous thrombosis is the most common form of infarction, resulting in focal neurologic deficits, increased ICP, and papilledema. Arterial infarction may involve large vessels, cause lacunar events, or result from septic emboli.[22]

Neurological disturbances in patients with Hodgkin's disease may result from involvement of the intracranial portion of the CNS, the spinal cord, or the peripheral nervous system (PNS). According to some authors, involvement of the nervous system in

patients with Hodgkin's disease occurs in 13 to 15% of all cases , although a review of 2,185 patients with Hodgkin's disease found only 12 (0.5%) who developed neurological symptoms, signs, or both .[23]This discrepancy may be related to increasingly early diagnosis and treatment of this condition. Most examples of neurological involvement are secondary, occurring from discrete or diffuse metastases via meningeal vessels or from direct tumor extension.

Ocular abnormalities associated with Hodgkin's disease include uveitis and retinopathy, keratitis sicca with bilateral enlargement of the parotid glands, and keratitis with vascularisation.

Because of its proximity to the base of the skull and its long extradural course, the Abducens nerve is the cranial nerve most commonly affected by multiple myeloma, and it is also commonly involved by plasmacytomas located at the base of the skull. The dysfunction may be unilateral or bilateral. It may be isolated, or it may occur in association with other cranial neuropathies, including optic neuropathy. Cranial nerves other than the abducens nerve, including the vestibulocochlear and trigeminal nerves and the other ocular motor nerves, can be damaged by multiple myeloma and plasmacytomas. As with Abducens nerve paresis, paresis of the oculomotor or trochlear nerves that occurs in these settings can be isolated or associated with other neurological abnormalities. The paresis may be the first sign of the disease, or it may occur late in the course of the disease. Rare cases of ocular motor nerve paresis are bilateral, thus mimicking an intrinsic brainstem process, but most are unilateral.

Orbit:

Orbital infiltrations are reported in leukemia. Orbital plasmacytoma can be the first manifestation in certain cases of multiple myeloma . All types of leukemia may involve the orbit; however, such involvement occurs more frequently in acute leukemia than in chronic leukemia. Leukemia is therefore not an infrequent cause of proptosis in children. Various authors report that 2 to 11% of children with proptosis have some form of acute leukemia. The orbital involvement may be related to infiltration of soft tissue by leukemic cells, to hemorrhage, or to both.

Orbital infiltration in leukemia causes proptosis, diplopia, edema of the eyelids, chemosis of the conjunctiva, and moderate to severe pain, thus mimicking an orbital cellulitis. It usually occurs in patients with previously diagnosed leukemia, but in some cases, it is the first evidence of the disease.

Leukemic cells may infiltrate almost all of the structures in the orbit, including the extraocular muscles, fat, and lacrimal gland.Leukemic infiltration may even extend beyond the confines of the orbit into the paranasal sinuses. It is usually diffuse, but in some patients, the infiltration produces a relatively well-circumscribed mass of leukemic cells. Although such a mass can accompany any form of leukemia and can be observed in patients with chronic leukemia after long periods of remission, it occurs most often in patients with acute myelogenous leukemia.

In such patients, the mass may have a characteristic greenish appearance caused by the pigmented enzyme myeloperoxidase and is called, as noted above, a granulocytic sarcoma or chloroma. The cause of granulocytic sarcoma is unknown, but cellular

immune deficiency may play an important role. Granulocytic sarcomas may appear at any time during the course of the leukemia and, like diffuse infiltration, may even occur months or even years before there is any evidence of other systemic disease. In patients with leukemia, bilateral involvement of the orbits is not uncommon. It is usually a poor prognostic sign.

Granulocytic sarcoma or chloroma is an unusual localized tumor composed of cells of myeloid origin. Involvement of the orbit and the ethmoid sinuses presenting as proptosis is rare [(22)].

Orbital involvement is a rare complication of Hodgkin's disease. The majority of cases occurs in patients with known Hodgkin’s disease and consists of infiltration of the eyelids, subconjunctival space, conjunctiva, soft tissues of the orbit, and lacrimal gland. Some patients with multiple myeloma may develop signs of an orbital process as the result of their myeloma. Such patients may present with proptosis, diplopia, visual loss, or a combination of these manifestations. Eye, brow, or orbit pain may be a prominent complaint, although this is by no means always the case.

Some of these patients have multiple myeloma at the time their orbital symptoms and signs develop, but in most, the orbital process is the first sign of the disorder. In these patients, myeloma cells usually infiltrate orbital soft tissue. The infiltration is often diffuse, affecting all of the tissues in the orbit, including fat, extraocular muscles, and lacrimal gland, but it also may be limited, presenting as focal enlargement of the lacrimal gland or as a well-defined mass. Orbital involvement is usually unilateral, but it may be bilateral.

POSTERIOR SEGMENT MANIFESTATIONS

The posterior segment manifestations of haematological malignancies can be divided into:

1) Direct manifestations (leukemic infiltrates),
2) Possible direct manifestations (such as white-centered retinal haemorrhages),
3) Manifestations of complications of malignancy
   (chiefly anemia, thrombocytopenia, and hyper viscosity states)
4) Opportunistic infections.
5) Chance or unrelated findings.

Leukemic retinopathy, the term most commonly used to denote the fundus manifestations of anemia, thrombocytopenia, and increased blood viscosity seen in patients with leukemia. In general, the term does not necessarily refer to frank leukemic proliferation. The changes of "leukemic retinopathy" may be more commonly seen with the acute leukemias but the frequency with which they occur has not been adequately studied to be certain. Although perivascular sheathing may be due to actual perivascular infiltrates, tortuous dilation of the retinal veins probably is not. The veins and arteries may assume a yellowish tinge both because of anemia and leukocytosis. Retinal hemorrhages may be seen, often at the posterior pole. The hemorrhages may be subretinal, deep retinal, superficial retinal, or preretinal, and there may be breakthrough bleeding into the vitreous cavity. They may have a blot or blotch shape, flame shape, or they may have white centers.

Cotton-wool spots may be the presenting abnormality that precipitates the systemic evaluation leading to the diagnosis of leukemia. The cotton-wool spots may be due to local factors, such as an abnormally large cell or cluster of cells occluding retinal arterioles, and may not be related to the overall peripheral blood composition. In general, hematologic parameters are not associated with the presence of cotton wool spots. Cotton-wool spots and hemorrhages can resolve in patients with chronic disease.

Retinal hemorrhages and cotton-wool spots related to anemia or thrombocytopenia are common in patients with non-Hodgkin's lymphoma, but direct retinal involvement of the retina in patients with systemic lymphoma is extremely rare. Hodgkin’s disease can cause periphlebitis, focal chorioretinitis, vitritis, and optic disc edema. Patients with "numerous white deposits in the retinal periphery," chorioretinitis, Roth's spots, and perivascular retinitis have been reported.

Rosenthal emphasized that optic nerve infiltration occurs predominantly in children with acute lymphocytic leukemia (ALL) and must be differentiated clinically from papilledema. Patients with leukemic infiltration of the prelaminar optic nerve typically have marked swelling of the optic disc with a fluffy superficial infiltrate and variable hemorrhage . The visual acuity may be minimally or severely affected. With retrolaminar optic nerve infiltration, moderate to marked disc elevation and edema with variable hemorrhage may be present and marked vision loss is generally observed.

Optic nerve infiltration may occur despite prophylactic brain irradiation in leukemia because of the shields employed to protect the eyes. In general, optic nerve infiltration by leukemia responds well to radiotherapy (with or without intrathecal

chemotherapy). Brown and co-workers reported the case of a patient with acute promyelocytic leukemia and optic disc infiltration who showed complete resolution with oral all trans-retinoic acid alone.

Retinal or preretinal infiltrates:

Leukoembolization of the retina with resulting ischemia from infarction of the retinal capillary bed is seen in numerous conditions manifesting as Purtscher's-like retinopathy . The mechanism of micro vascular occlusion in these diseases is generally believed to be leukocyte aggregation resulting from activation of complement factor C5a.

This aggregation hypothesis is supported by evidence of increased blood viscosity and leukostasis in the vasculature of brains of patients who have died from leukemia [(7)]. The clinical presentation of severe peripheral retinal ischemia may be due to unrecognized leukoembolization of the retinal vasculature prior to the diagnosis of CML. The progressive retinal ischemia may exacerbate the secretion of angiogenic factors in the diseased retina and may lead to accelerated development of neovascular disease.

Interestingly, recent studies have found that systemic blood plasma concentrations of angiogenic factors, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are significantly increased in patients with CML, compared to healthy controls [(8,9)]. Extravascular leakage of circulating VEGF and bFGF from incompetent vessels into the compromised retina may also act to increase the local tissue levels of these angiogenic factors and accelerate the clinical course of proliferative disease.

Leukemic infiltrates have been described by Kuwabara. A patient with chronic myelogenous leukemia with large gray-white nodules of varying sizes in the retina was reported. Gray-white streaks along vessels may be caused by perivascular leukemic infiltrates. Infiltrates are also observed in the retina in systemic lymphomas also.

Choroidal infiltrates:

Although the choroid is probably the most commonly affected part of the eye in leukemias, clinical signs of choroidal involvement are often subtle unless there is overlying retinal changes which bring them to attention. Serous retinal detachment overlying choroidal infiltrates or overlying frank choroidal masses are important clues. Serous retinal detachment overlying areas of choroidal infiltration have been reported in patients with CLL, ALL, CML and AML.

Serous retinal pigment epithelial (RPE) detachment has also been reported in a patient with acute lymphoblastic leukemia. The serous retinal and RPE detachments can be the presenting manifestation of the leukemia. Eventually, as the changes resolve, coarse clumping of the RPE is seen. Areas of RPE hyperplasia including heaped-up masses of pigment epithelium surrounding leukemic cells. The choroid is commonly infiltrated by leukemic cells during the course of both acute and chronic leukemia. In fact, Leonardy et al. found the choroid to be the most frequently involved site (31.1%) of ocular involvement in an autopsy series of leukemic patients. Abnormalities that are visible during ophthalmoscopy, however, are rare. Nevertheless, some patients develop generalized serous detachment of the retina, retinal pigment epithelium, or both, associated with diffuse infiltration of the choroid by leukemic cells. Others develop

localized choroidal masses with overlying retinal and RPE detachment, and rare patients develop pigmentary changes in the RPE from interference of the blood supply to the RPE by leukemic cells that infiltrate the choroid.

Vitreous infiltrates:

Vitreous opacities may be manifestations of an intraocular malignancy. Moribund patients may show massive collections of tumor cells in the vitreous, but most patients with intravitreal hemorrhage have neoplastic cells in the vitreous only because their peripheral blood contains tumor cells. The cells do not appear to be preferentially replicating in the vitreous cavity. Leukemic cells have been found in the vitreous of patients with neovascularization of the disc. Disc neovascularization has also been seen in a patient with erythroleukemia although that patient also had diabetes. Vitreous involvement has been seen at the time of autopsy in patients with reticulum cell sarcoma, Burkitt's lymphoma, multiple myeloma, and Hodgkin's disease In leukemia the internal limiting membrane usually acts as a barrier to infiltration of the vitreous by leukemic cells; however, such infiltration occasionally occurs. Terson syndrome occurs in rare cases.

White-centered retinal hemorrhages (Roth spots):

Most patients are asymptomatic or have visual loss related to the underlying disease process. White-centered retinal hemorrhages may be isolated or more numerous. Depending on the association, white-centered hemorrhages most likely result from localized capillary rupture from any anoxic insult or sudden elevation in venous pressure. The white center is a fibrin platelet aggregate that results during the physiologic healing

process. The collections of abnormal cells are white blood cells (in leukemia/lymphoma) or platelets (in multiple myeloma). The most common underlying factors are anemia and thrombocytopenia.

Manifestations of hyper viscosity:

Whole-blood hyper viscosity may lead to veno-occlusive disease, micro aneurysm formation, retinal hemorrhages, and retinal neovascularization. The most common manifestation is probably a mild or "hyperpermeable" central retinal vein occlusion. A systemic hyper viscosity state should be suspected in patients with bilateral changes. Peripheral retinal neovascularization has been reported in patients with CML in association with peripheral capillary nonperfusion. Most cases have associated extreme leukocytosis or thrombocytosis. Presumably, the hyperviscosity state leads to peripheral nonperfusion and subsequent development of retinal neovascularization. In general, the blood viscosity begins to increase remarkably only with white blood cell counts of greater than 50,000. In multiple myeloma, increased viscosity results in reduced flow of blood through the eyes and produces the characteristic changes of dilatation of the retinal arteries and veins, hemorrhages, microaneurysms and areas of capillary closure.

Micro aneurysm formation may be apparent, most frequently in the retinal periphery and mid periphery. If hyper viscosity is severe, retinal changes similar to those described in Waldenström's macroglobulinemia may be seen. Serous and exudative retinal detachments associated with multiple myeloma have also been reported. Reduction in the abnormalities producing hyper viscosities can reverse retinal changes.

Optic Neuropathy:

In multiple myeloma, the initial clinical manifestation is usually bilateral optic disc swelling. The infiltration of optic nerve meninges by malignant plasma cells and impaired vascular supply by intraluminal plasma cells and monoclonal hypergammaglobulinemia is the mechanism behind optic neuropathy. The infiltration and compression of optic nerve causes visual loss in myeloma.

In acute lymphoblastic leukemia also, optic nerve head infiltration is seen. Leukemic infiltration of orbital portion of optic nerve is usually a preterminal phenomenon in the past but now by the use of prophylactic CNS irradiation and chemotherapeutic agents , the long term survival has improved and the leukemic invasion of optic nerve has become uncommon and has become a treatable cause of vision loss.In acute leukemias especially , the lymphocytic type , clinical evidence of infiltration of orbital portion of the optic nerve is common.

Histopathologically, the optic nerve infiltration is only marginally more common in acute than chronic leukemia. Mostly at the time of optic nerve head infiltration ,there is CNS involvement or active bone marrow disease but it may also be the first manifestation of relapse or recurrent leukemia.

Two patterns of leukemic infiltration are:

1. Retro laminar (which is common) and
2. Pre laminar .

In the pre laminar and laminar involvement, there is fluffy, whitish infiltrate in the substance of the disc, along with disc swelling and hemorrhage. If the infiltrate does not include the macula the central visual acuity is retained or minimally reduced.

In the retro laminar involvement, fluffiness is almost absent in such cases, but an associated retinopathy that includes evidence of both arterial and venous occlusion may be present.

Although leukemic infiltration of the retro laminar portion of the optic nerve may be compatible with normal visual function, there is usually moderate to severe loss of vision. Because both patterns of leukemic infiltration of the optic nerve are associated with some degree of optic disc swelling, they must be differentiated from papilledema. In many cases, this is extremely difficult, not only because in all three settings there is optic disc swelling associated with minimal if any visual loss, but also because it is not unusual for optic nerve infiltration to occur simultaneously with meningeal infiltration and increased ICP , particularly in the setting of treatment of acute promyelocytic leukemia with all-trans retinoic acid .

For this reason, in all patients who present with optic disc swelling in the setting of leukemia, neuroimaging studies and a lumbar puncture must be performed. Both CT scanning and MR imaging typically show generalized enlargement of the affected optic nerve often associated with a cuff of enhancement surrounding the nerve that represents leukemic cells. Ocular echo graphy may also be helpful in this setting, showing that the nerve itself is enlarged.

TREATMENT OF OCULAR INVOLVEMENT IN MALIGNANT DISORDERS:

The treatment of leukemia is discussed below; however, it is appropriate here to emphasize that the optimum treatment for infiltration of the optic nerve is prompt local irradiation. This is typically performed urgently and followed by intrathecal as well as systemic chemotherapy.

Patients who receive about 2000 cGy to the posterior globe and orbit usually show a rapid resolution of their disc swelling and infiltration that may be accompanied by improvement in vision.

In addition to infiltration, neovascularization of the optic disc occurs in patients with acute leukemia, particularly in the lymphocytic type.

An optic chiasmal syndrome may be produced by a plasmacytoma that mimics a pituitary adenoma. Homonymous field defects in patients with multiple myeloma may result from compression or infiltration of the post chiasmal visual sensory pathways by myeloma cells, or from secondary effects of the disease (e.g., infarction of the occipital lobe), or from infectious complications of the disease, its therapy, or both (e.g., intracranial abscess formation).

OPPORTUNISTIC INFECTIONS:

Potentially life threatening infections unusually occur during periods of neutropenia in patients with leukaemia , which may be result of either chemotherapy of due to the underlying disease. A wide variety of infections by bacterial, viral, fungal and protozoal organisms are known to occur in these patients.

Cytomegalovirus(CMV) is one of the common viruses infecting immunocompromised host, considerably involving the neuroectodermal tissue. CMV virus invades the retina causing retinal necrosis, haemorrhage, vascular sheathing and combined rhegmatogenous and exudative retinal detachment. Other viruses causing necrotising retinitis in immunocompromised hosts are herpes simplex, varicella and mumps virus. Granulomatous uveitis has been reported to occur in mumps.

Peripheral corneal ulcer, keratitis and scleritis are found to occur in herpes zoster. Fungal causes of ocular infection are common in leukaemias. Uveitis and retinitis with characteristic cotton balls in vitreous occurs in candida infection. Aspergillus infection is also common in leukemic patients.

Pseudomonas infection is common in immunocompromised leukaemic patients starting occasionally as blepharoconjunctivitis which spreads causing orbital cellulitis. Sweet's syndrome is worth mentioning in this context which is characterised by sudden fever, neutrophilic leucocytosis , erythematous and tender pseudo vesiculated plaques or nodules that readily respond to corticosteroid therapy Endophthalmitis with potentially lethal effects upon visual potential is also recognised to occur in acute leukaemia.

TOXICITY TO ANTILEUKAEMIC DRUGS

Many novel anticancer drugs have been introduced in the past few years , both in research protocols and in routine clinical practice. Full range of side effects is not known still for many of these. A few important drugs causing ocular side effects will be mentioned here. Posterior sub capsular cataract has been reported to occur with busulphan.

Vincristine and vinblastine clinically affects the motor nerves of the eye (CN III, IV,VI & VII), are toxic to CNS and causes corneal hypoaesthesia. Vincristine causes optic atrophy. Cystosine-Arabinoside topically or systemically has been shown to be toxic to the corneal epithelium.

Patients on cyclosporine often receive other drugs causing dystonic eye movements which can delay the diagnosis and treatment resulting in irreversible neurological defect and hence recognition of this association is very important.

Patients with leukemia may develop neurological dysfunction from the toxic effects of drugs used to treat the leukemia and from infections that occur in the CNS of patients who are debilitated or immune suppressed. With conventional cranial radiotherapy, neurotoxicity is more often sub acute and delayed, rather than acute.

Intrathecal methotrexate may cause chemical meningitis. A sub acute leukoencephalopathy occurs in patients treated with methotrexate and is thought to be caused by direct toxicity of the drug. It is more commonly encountered when methotrexate is given in high doses intravenously and intrathecally and/or combined with

cranial irradiation, and it occurs in up to 50% of children undergoing such therapy. Other drugs may produce a similar encephalopathy, a peripheral neuropathy, or both

BONE MARROW TRANSPLANT (BMT)/ GVHD

Bone marrow transplantation may follow development of ocular symptoms and signs , either due to radiation treatment or GVHD occurring along with it. Ocular problems are more frequently recognised due to the recent improvements in systemic management of these patients. GVHD leads to ocular manifestations like cicatricial lagophthalmos, ectropion of lid, keratoconjunctivitis sicca , sterile and pseudo membranous conjunctivitis, corneal epithelial defects, corneal ulceration and melting and uveitis. Corneal keratinisation may occur in severe cases. Cataracts commonly occur after autologous bone marrow transplantation.

Patients with chronic GVHD manifest frequently than patients with acute GVHD. Severe chronic GVHD is associated with severe ocular complications leading to poorer survival. Sjogren syndrome or scleroderma like crisis are often the presenting features of chronic GVHD. The picture of acute and/or chronic transplant reaction of the host cells against grafted bone marrow has become more frequent since the era of BMT.

Acute GVHD of conjunctiva occurs in four stages namely injection/ exudation and chemosis / formation of pseudomembranes / defects of the corneal epithelium. Fibrotic Arlt lines of the tarsal conjunctiva is a pathognomonic sign for chronic GVHD. Thus screening for ocular sicca should be done in asymptomatic patients and artificial tear replacement must be initiated.

Impairment of visual acuity following BMT commonly occurs due to cataract formation, probably related to steroid intake and total body irradiation for pre-transplant conditioning. Ocular manifestations of BMT are not uncommon in children, most common anterior segment problem being the rear film dysfunction.

Posterior segment involvement is less common to occur; unilateral epiretinal membrane and or bilateral discrete multiple chorioretinal hypo pigmented lesions in the middle to peripheral part of retina are found to occur. The most important complication anticipated is amblyopia in immature eyes is probably due to the high incidence of cataract.

Ischaemic retinopathy is also found to occur following BMT. The aetiology is unclear, probably multifactorial, related to treatments like cyclosporine or radiation.

PART - II

AIMS AND OBJECTIVES:

1. To observe the incidence and types of retinopathy in various disorders of blood.
2. To determine the diagnostic and/or prognostic importance of lesions seen
3. To study the progression / resolution of lesions with treatment of blood dyscrasias

STUDY DESIGN:

200 eyes of 100 patients were examined in this prospective, comparative, Hospital- based study.

MATERIALS & METHODS:

100 patients diagnosed with blood dyscrasias presenting at Stanley Medical College Department of ophthalmology, and other patients referred from allied departments were enrolled in the study

This study was done in accordance with the rules of the ethical committee.

All patients were informed about the purpose of the study and written and informed consent was obtained.

Patients falling within the inclusion criteria were included in the study. A detailed history taking and detailed physical evaluation. The evaluation was done after obtaining informed written consent in the patients' own language.

Ocular evaluation included:

- Recording best corrected visual acuity
- Anterior segment examination using Slit lamp
- Intraocular pressure measurement by Goldman Applanation Tonometry

- Field charting with Octopus analyser
- Dilated fundus examination by means of direct and indirect ophthalmoscope
- Fundus photography.
- Fundus Fluorescein angiogram , performed when indicated.

The patients also underwent relevant haematological investigations to find out the type of haematological disorders and its correlation with the clinical picture.

These patients were followed every two months with detailed ocular examination for the evolution of lesions, till resolution.

INCLUSION CRITERIA:

- All cases of newly diagnosed Blood dyscrasias.
- All age groups

EXCLUSION CRITERIA:

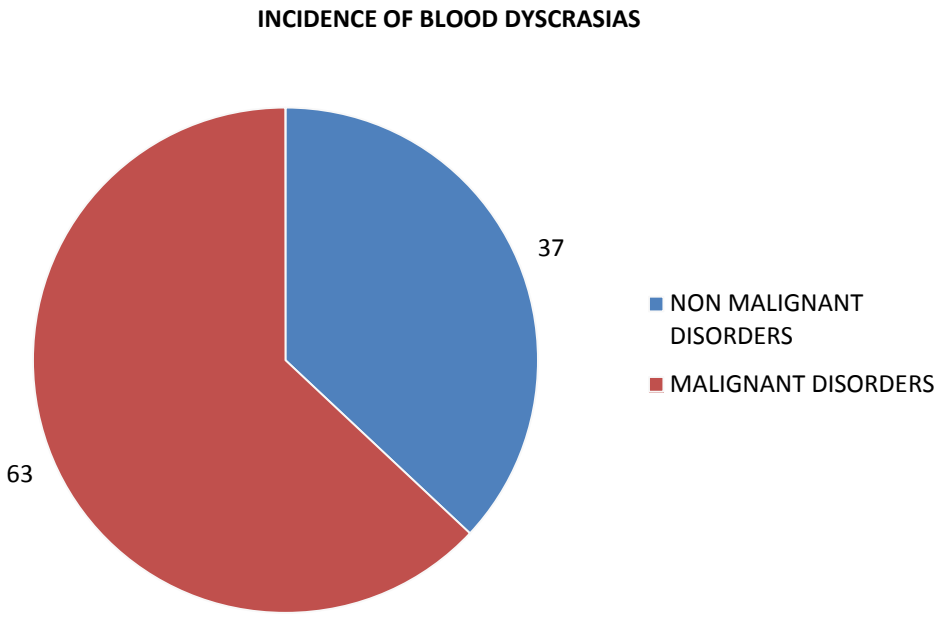
- Patients with associated systemic diseases such as diabetes, hypertension.
- Patients with ocular trauma.
- Patients with other ocular diseases(Eg, CRVO ,Eale’s disease)

OBSERVATION:

100 patients were included in our study.

Out of which, 37 were non- malignant and 63 malignant disorders of the blood.

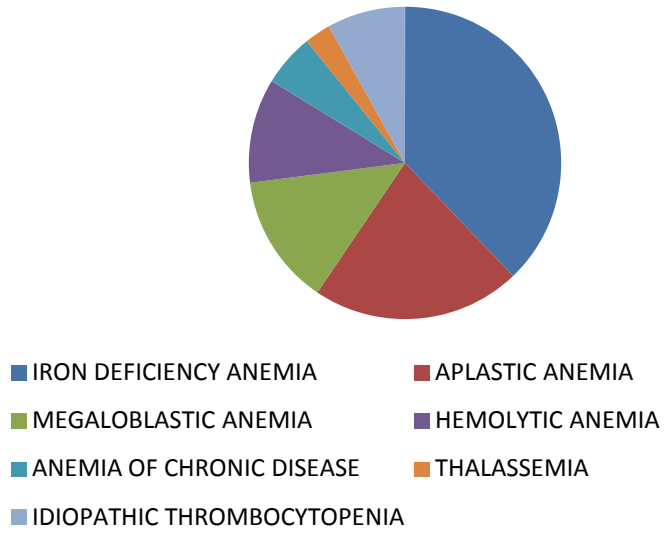
TOTAL	NON MALIGNANT DISORDERS	MALIGNANT DISORDERS
100	37	63



NON- MALIGNANT DISEASES:

The following were the non - malignant diseases observed. Commonest disorders of non- malignant etiology were anemias of which Iron-deficiency was the most common followed by Aplastic Anemias.

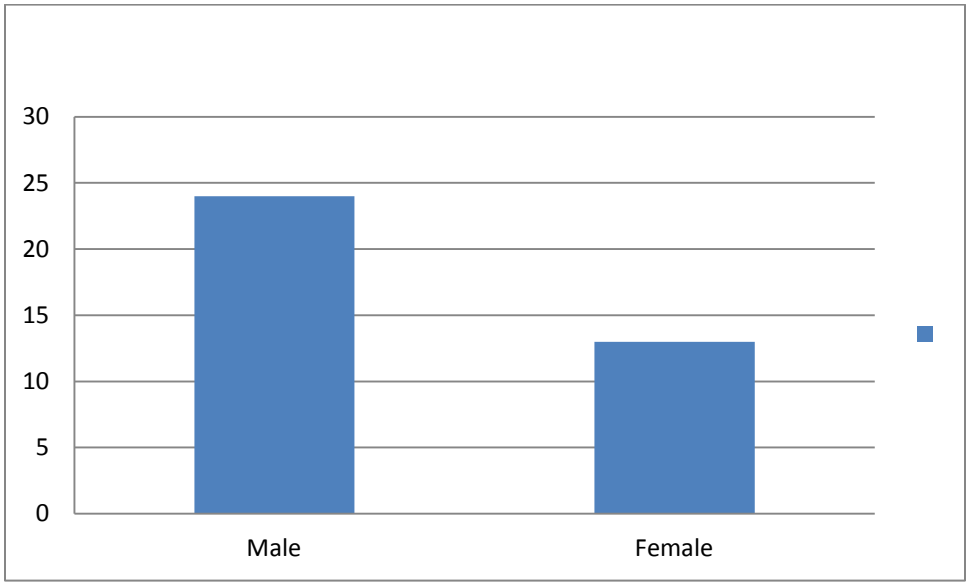
DISEASES	NUMBER OF PATIENTS
IRON DEFICIENCY ANEMIA	14
APLASTIC ANEMIA	8
MEGALOBLASTIC ANEMIA	5
HEMOLYTIC ANEMIA	4
ANEMIA OF CHRONIC DISEASE	2
THALASSEMIA	1
IDIOPATHIC THROMBOCYTOPENIA	3



1.SEX DISTRIBUTION:

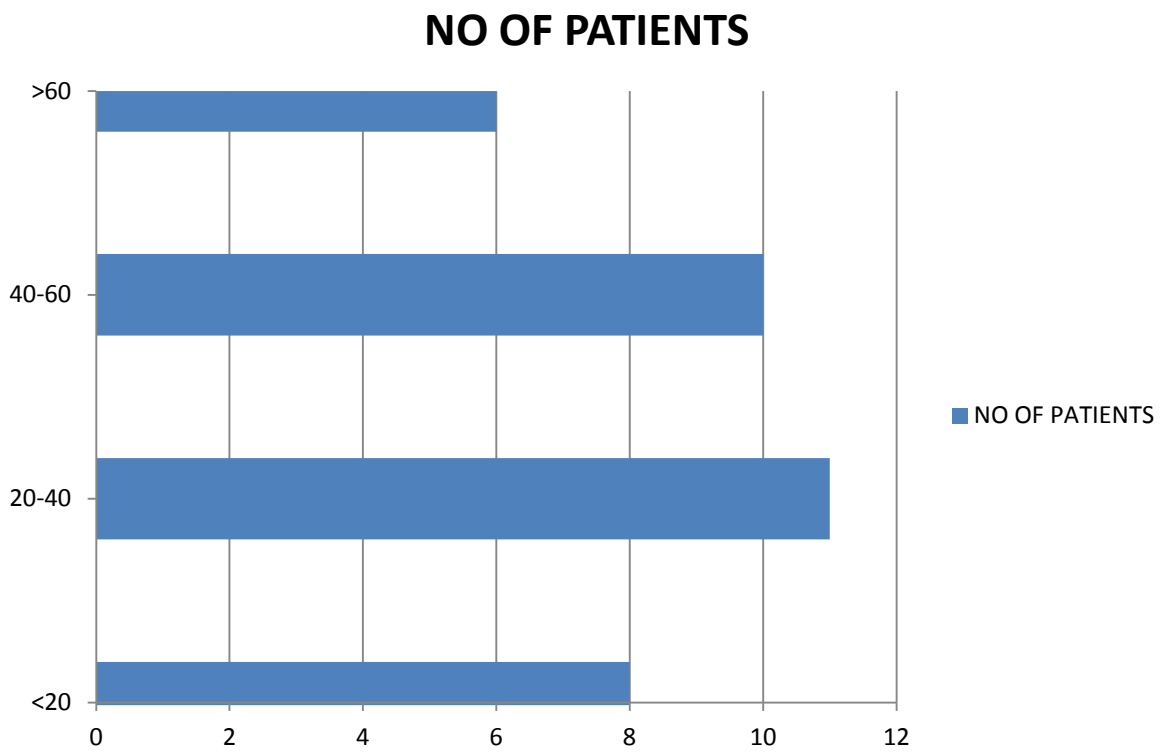
Among the 100 patients, with non malignant disorders, 24 were male and 13 female, while among malignant disorders 40 were male and 20 female.

NON MALIGNANT DISORDERS	
Male	Female
24	13



2.AGE INCIDENCE:

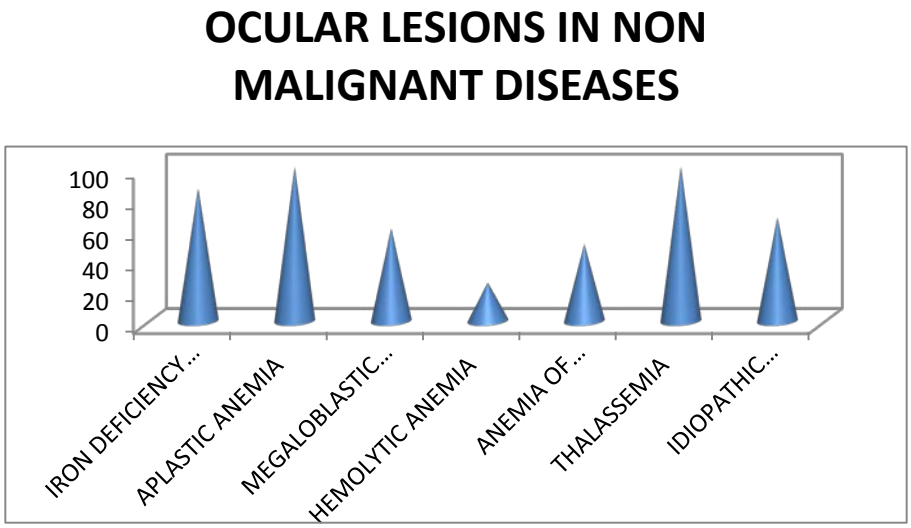
AGE GROUP	NO OF PATIENTS	OCULAR FEATURES	PERCENTAGE
<20	8	5	63%
20-40	11	11	100%
40-60	10	7	70%
>60	6	2	33%



Non malignant disorders of the blood were most common in the age group of 20- 40 yrs (32%) with all 11 patients in the age group demonstrating ocular lesions.

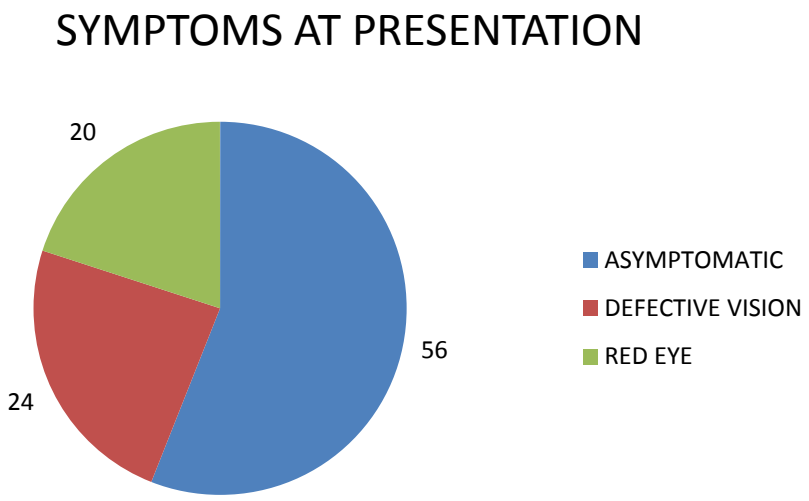
3. INCIDENCE OF OCULAR FEATURES IN NON MALIGNANT DISORDERS

DISEASES	NO OF PATIENTS	OCULAR FINDINGS	PERCENTAGE
IRON DEFICIENCY ANEMIA (IDA)	14	12	86%
APLASTIC ANEMIA (AA)	8	8	100%
MEGALOBLASTIC ANEMIA (MA)	5	3	60%
HEMOLYTIC ANEMIA (HA)	4	1	25%
ANEMIA OF CHRONIC DISEASE (ACD)	2	1	50%
THALASSEMIA (THAL)	1	1	100%
IDIOPATHIC THROMBOCYTOPENIA (ITP)	3	2	67%



3. SYMPTOMS AT PRESENTATION:

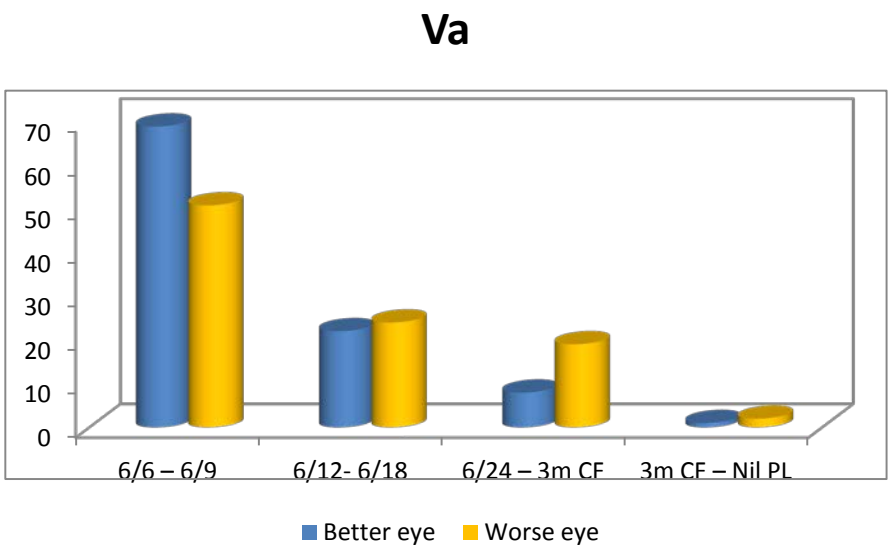
SYMPTOMS AT PRESENTATION	NO OF PATIENT	PERCENTAGE
ASYMPTOMATIC	19	56%
DEFECTIVE VISION	8	24%
RED EYE	7	20%



Most patients who presented with anemia were asymptomatic 19 (56%) , while 11patients (29%) had some complaints of defective vision while 7 patients (15%) had complaints of red eye due to sub-conjunctival haemorrhages.

4. **VISUAL ACUITY AT PRESENTATION:**

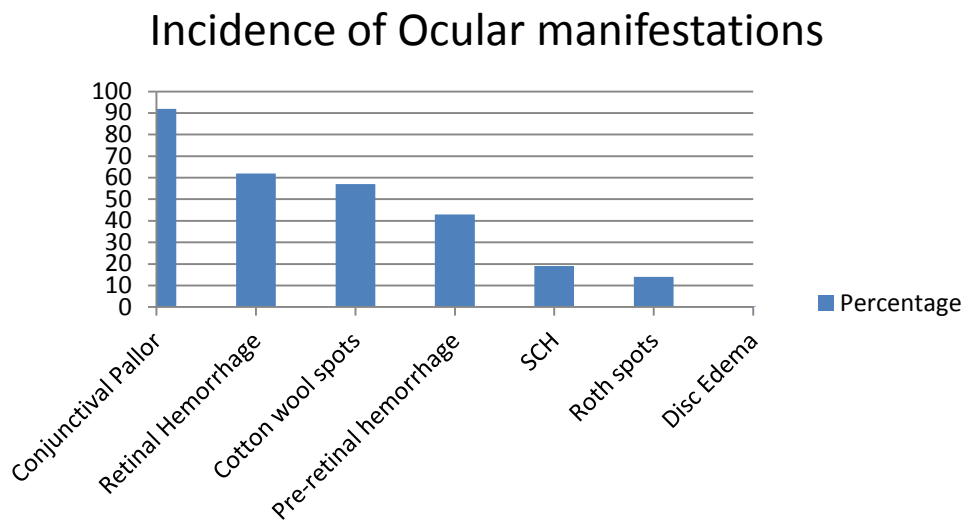
Vision	Better eye	Worse eye
6/6- 6/9	33(61%)	20(37%)
6/12- 6/18	11(20%)	10(18%)
6/24 – cf 3m	9(16%)	7(13%)
Cf 3m – PL	3(5%)	1(2%)



27 patients (73%) of non malignant diseases of the eye had good visual acuity (6/6 – 6/18) at presentation , while 10 (27%) eyes showed poor visual acuity , due to preretinal hemorrhage,involving the macula and disc edema in one case.

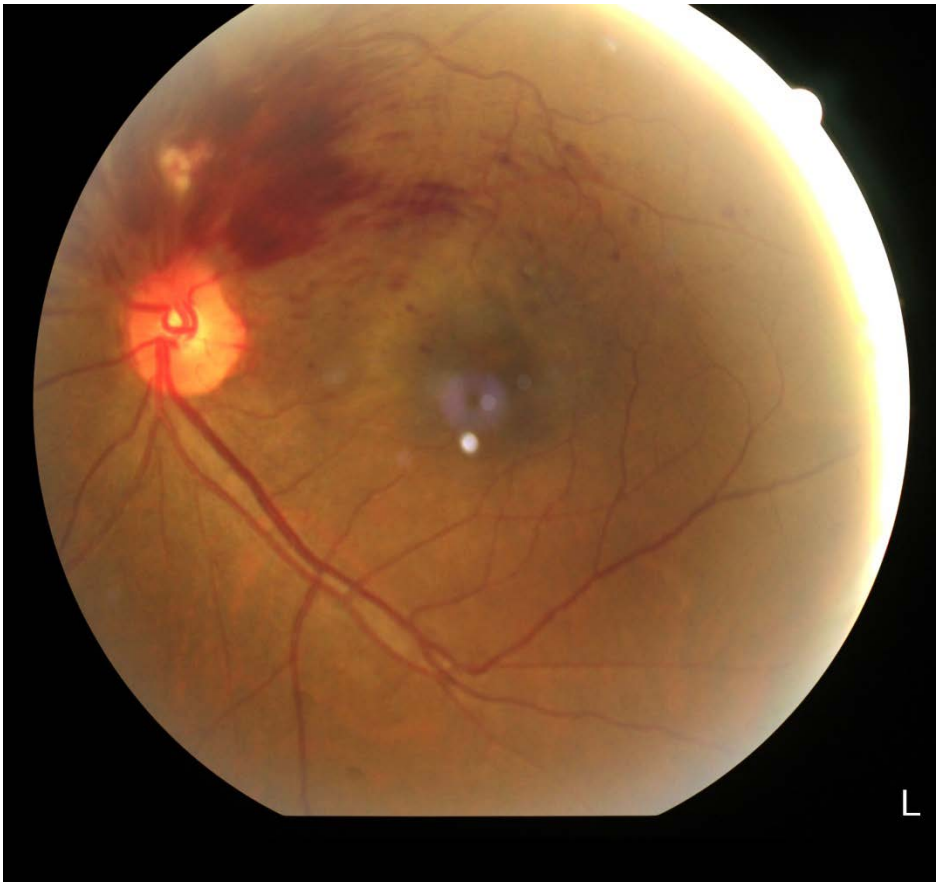
5. INCIDENCE OF OCULAR MANIFESTATIONS:

Ocular manifestation	No. of cases	Percentage
Conjunctival Pallor	34	92%
Retinal Hemorrhage	23	62%
Cotton wool spots	21	57%
Pre-retinal hemorrhage	16	43%
Roth spots	5	14%
SCH	7	19%
Disc Edema	1	0.3%

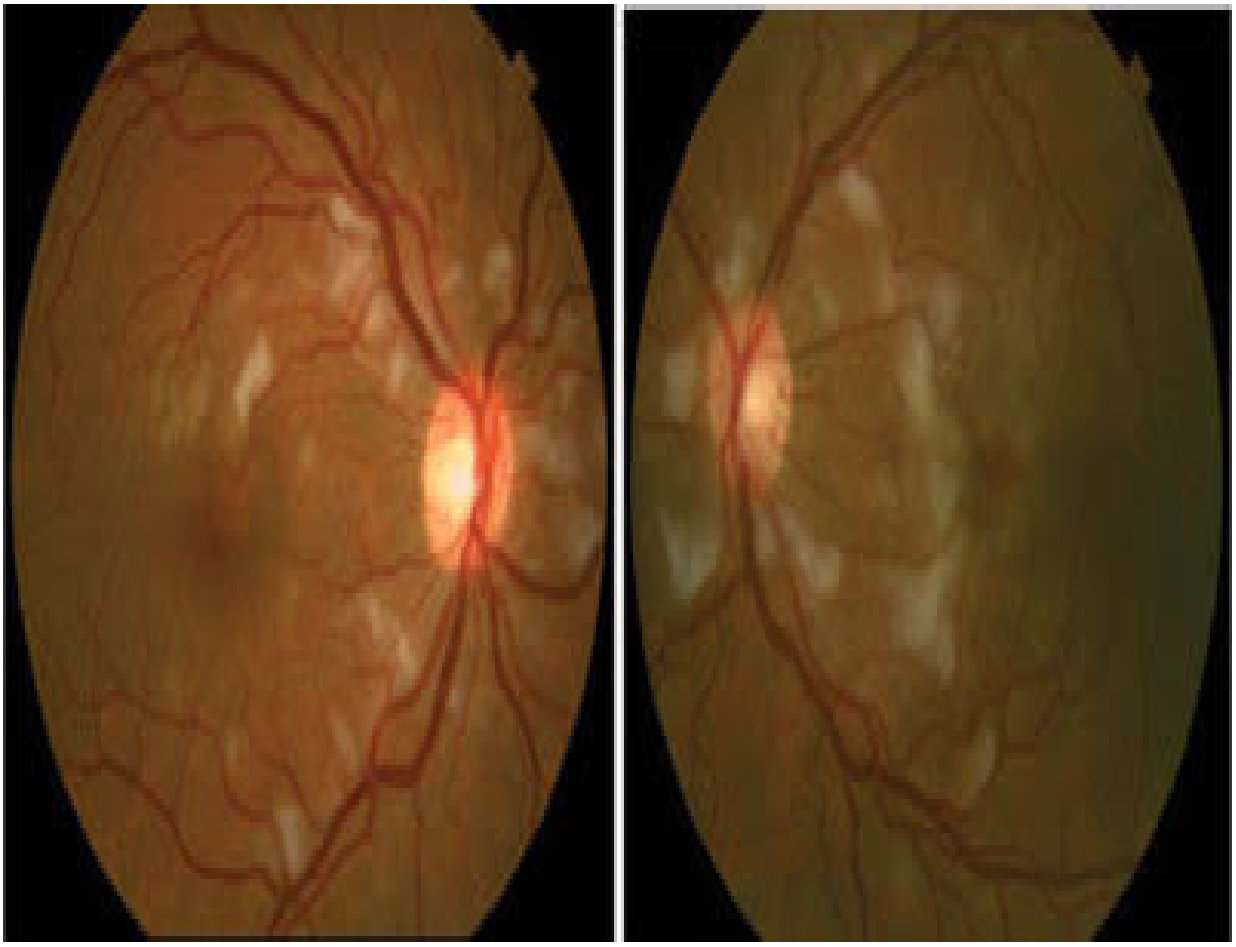


Non malignant diseases had conjunctival pallor (92%) as the most common manifestations followed by retinal hemorrhage (67%) and cotton wool spots (52%) . One case of unilateral disc edema was noted(0.3%).

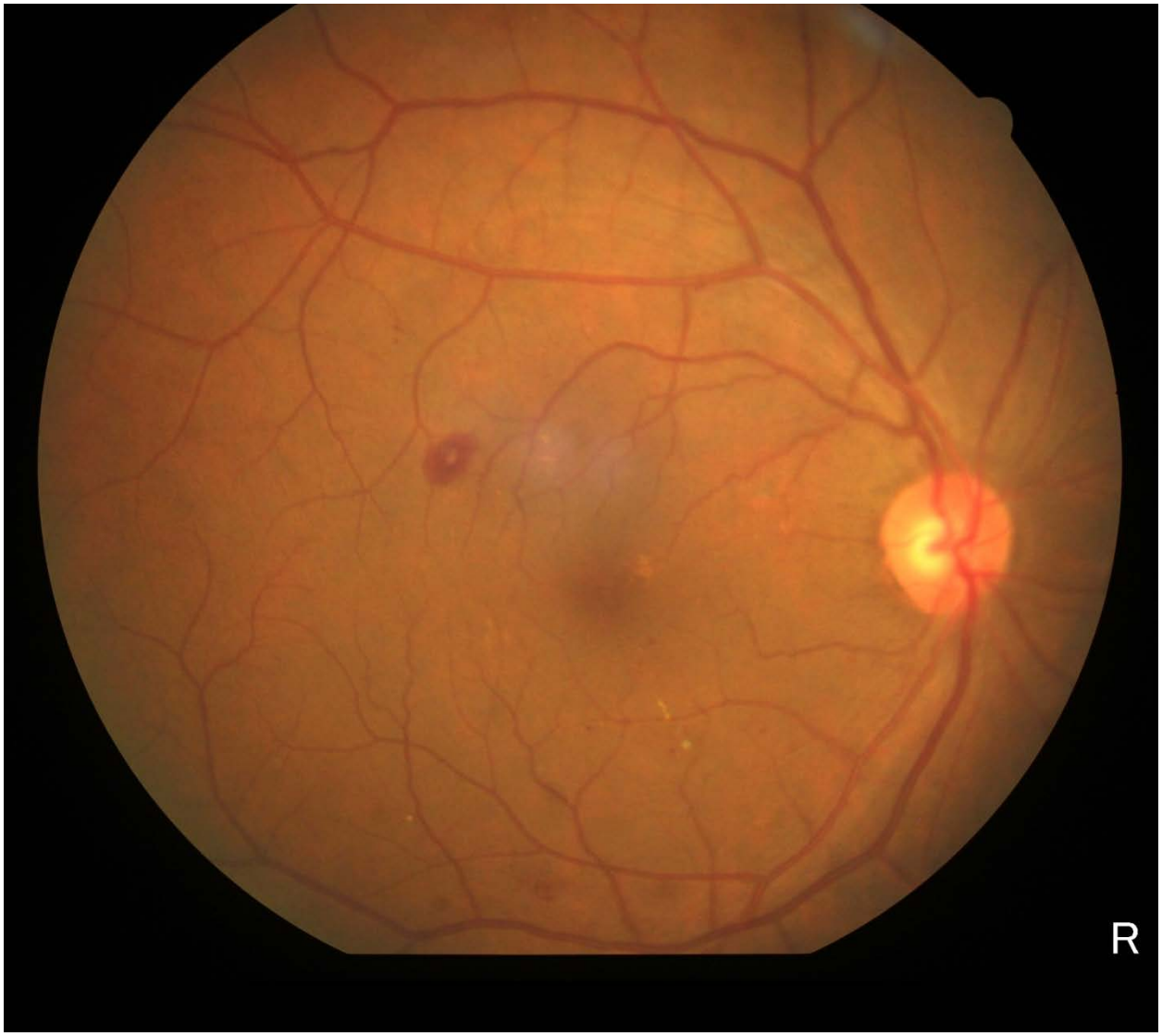
RETINAL HEMORRHAGES



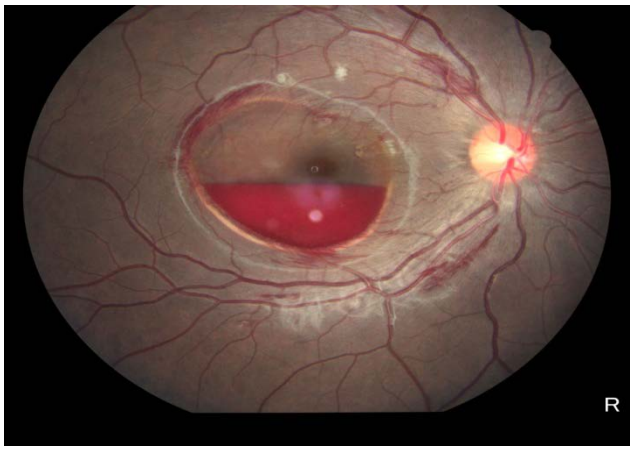
COTTON WOOL SPOTS

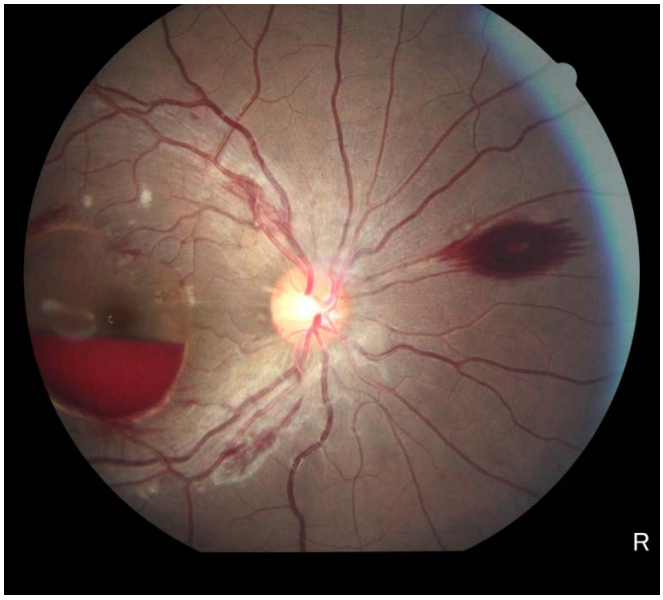


ROTH SPOTS

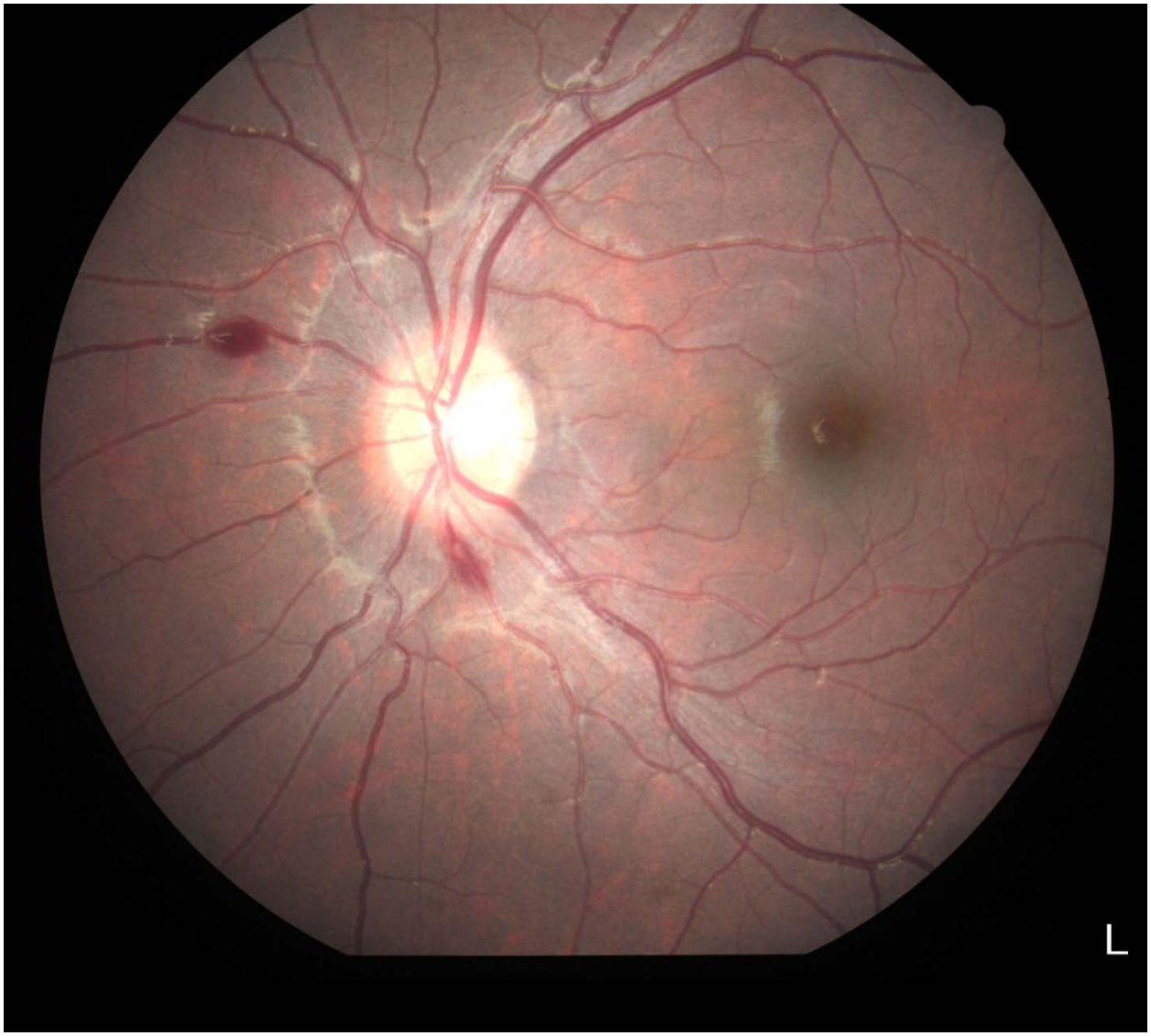


PRE – RETINAL HEMORRHAGES



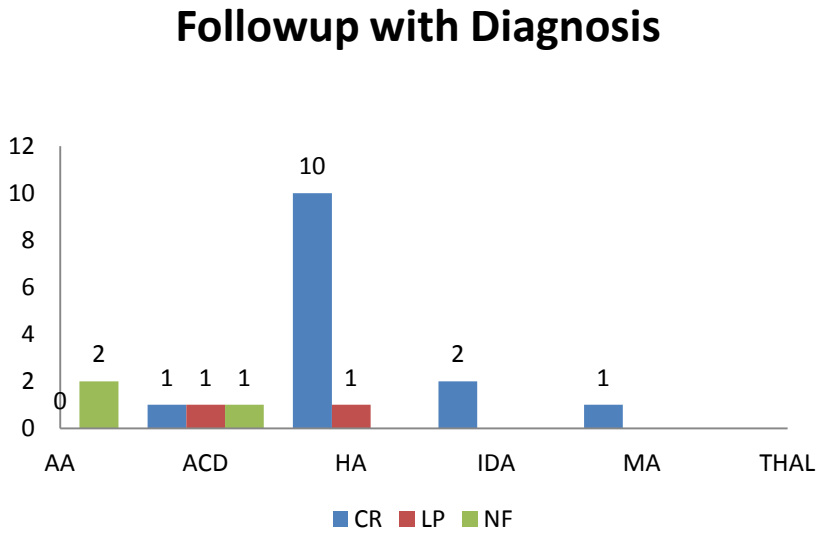


DISC OEDEMA



7.RESOLUTION OF LESIONS AND FOLLOW UP:

		RESOLUTION AND FOLLOW UP							
		AA	ACD	HA	IDA	MA	THAL	ITP	Total
Complete Resolution		6		1	10	3	1	1	22
Lesion Persisted		0	1		1			0	2
No follow Up		2			1			1	4
Total		8	1	1	12	3	1	2	28

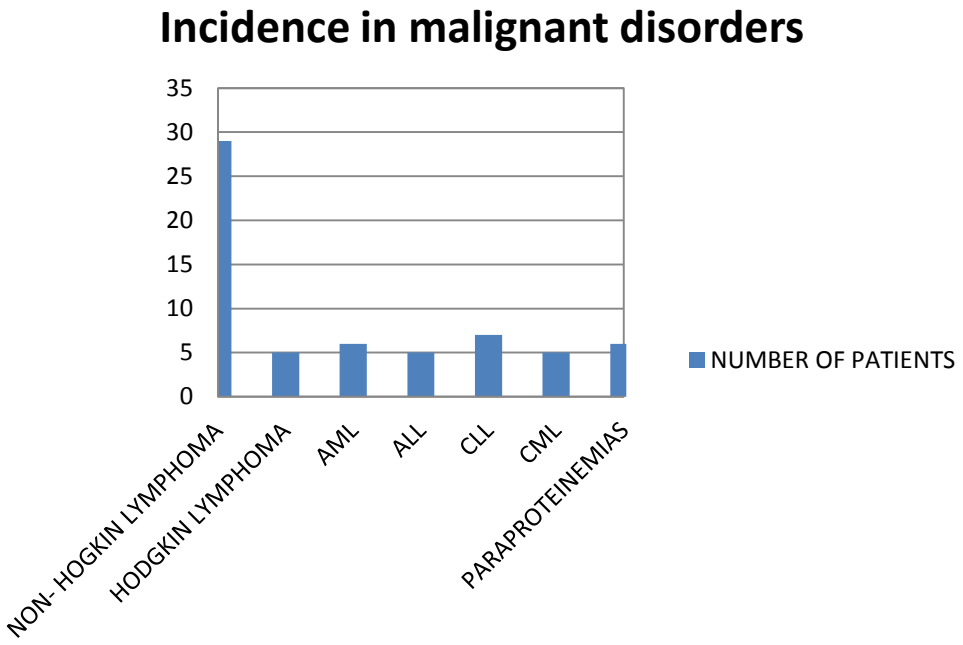


Most non malignant disorders showed resolution except two, one a case of severe iron deficiency with poor adherence to treatment and other with aplastic anemia due to underlying disease.

MALIGNANT DISEASES:

The malignant diseases enrolled in the study are :

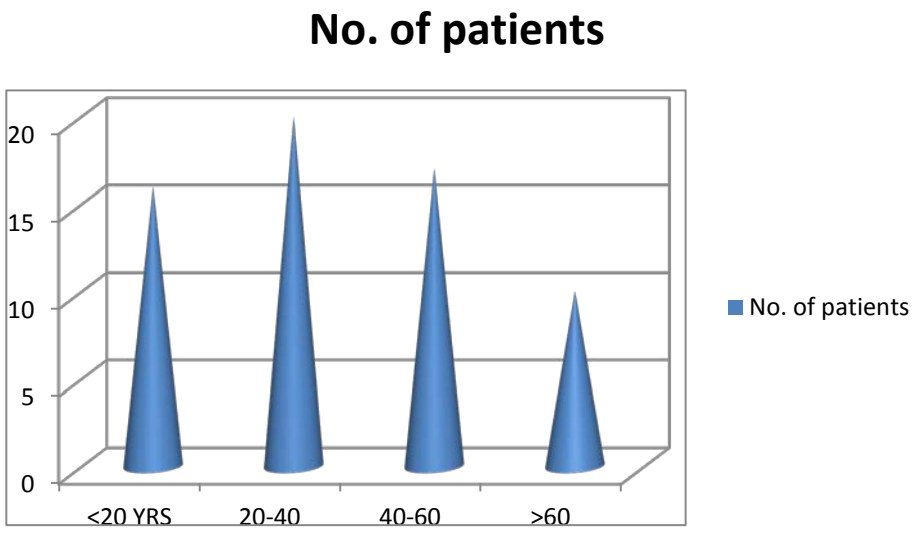
DISEASES	NUMBER OF PATIENTS	PERCENTAGE
NON- HOGKIN LYMPHOMA	29	46%
CLL	7	11%
AML	6	9.5%
PARAPROTEINEMIAS	6	9.5%
HODGKINS LYMPHOMA	5	8%
CML	5	8%
ALL	5	8%



Non- Hodgkin's lymphoma was the most common malignant disorder in our study.

1. AGE INCIDENCE:

AGE GROUP	NO. OF PATIENTS	PERCENTAGE
<20 YRS	16	25%
20- 40	20	32%
40- 60	17	27%
>60	10	16%

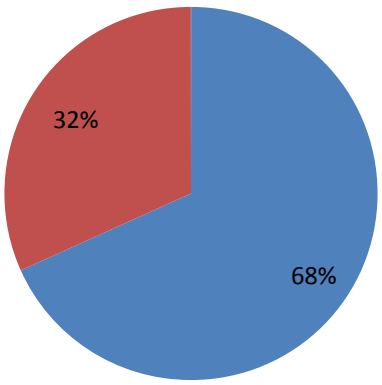


Malignant haematological disorders were most commonly seen in the age group of 20 – 40 years (32%).

2.SEX DISTRIBUTION:

MALIGNANT DISORDERS	
Male	Female
43	20

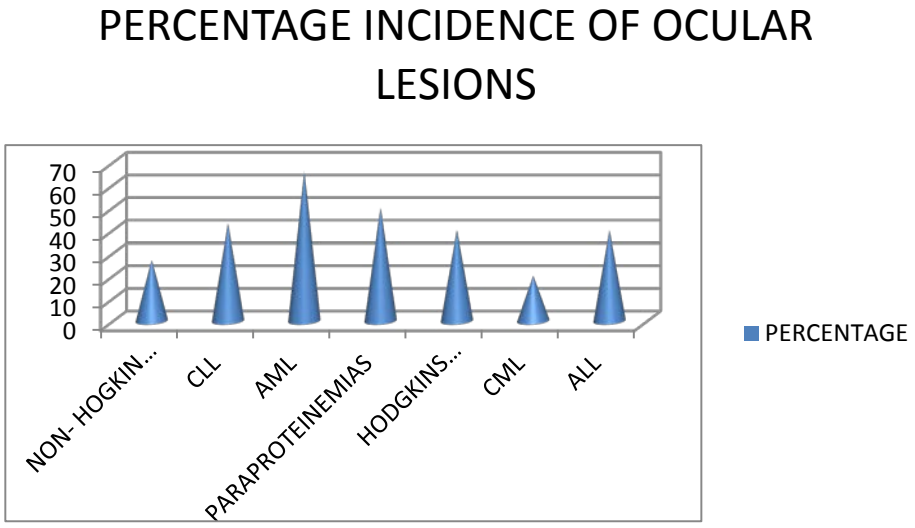
SEX DISTRIBUTION AMONG MALIGNANT DISORDERS:



Malignant Disorders of the blood are more common in males (68%)

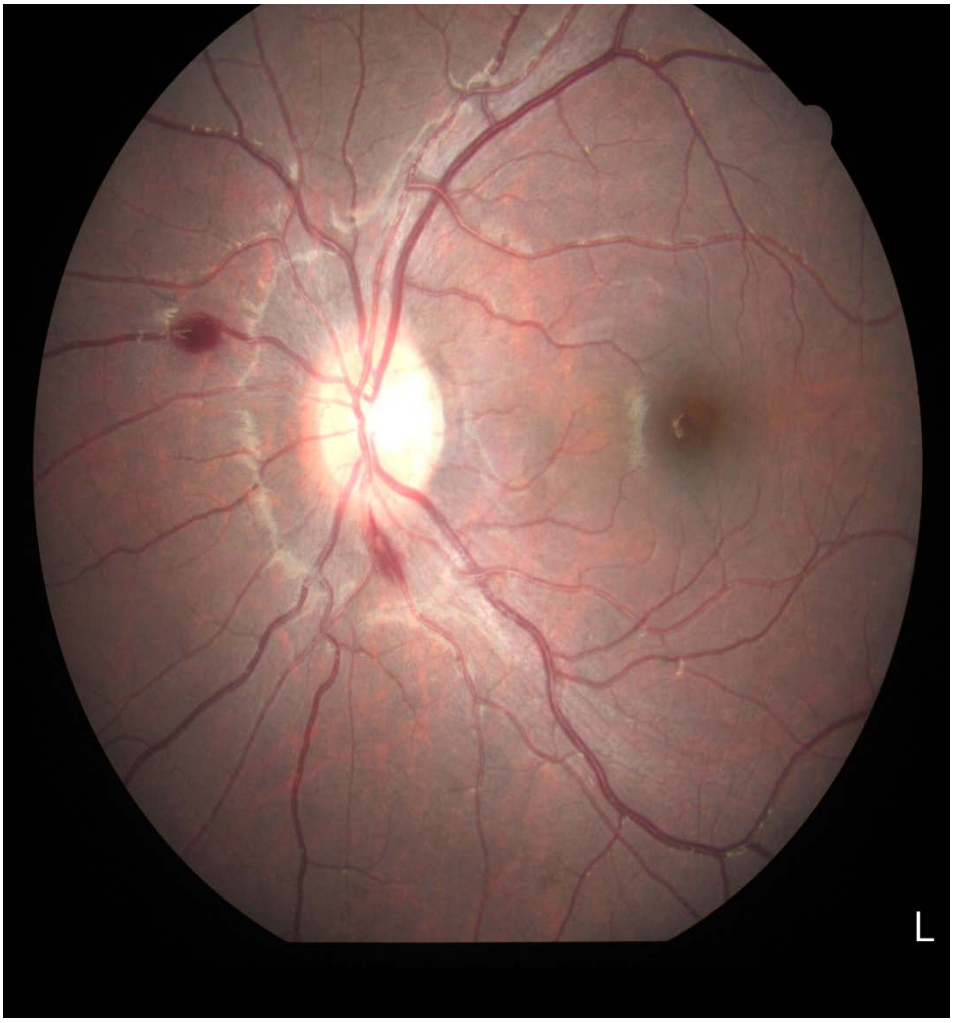
3.INCIDENCE OF OCULAR FEATURES IN EACH MALIGNANCY

DISEASES	NO. OF PATIENTS (63)	LESIONS PRESENT (23)	PERCENTAGE
NON- HOGKIN LYMPHOMA	29	8	27%
CLL	7	3	43%
AML	6	4	66%
PARAPROTEINEMIAS	6	3	50%
HODGKINS LYMPHOMA	5	2	40%
CML	5	1	20%
ALL	5	2	40%

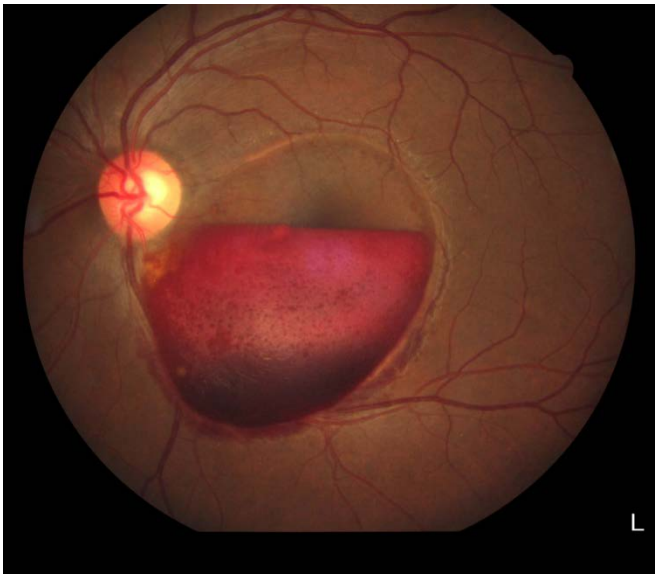


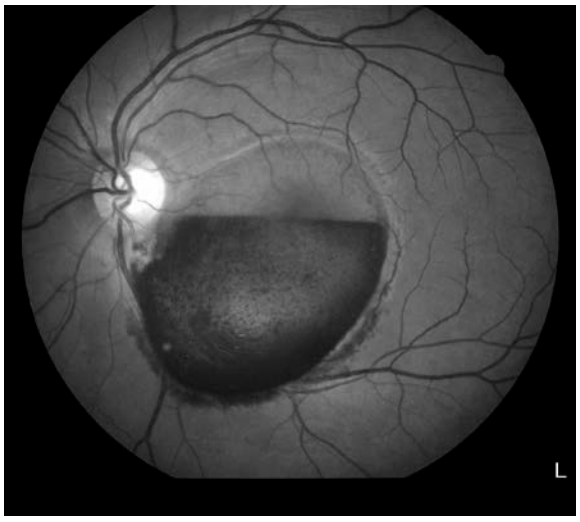
Ocular findings were most commonly observed in cases of acute leukemias, AML and ALL followed by paraproteinemias.

RETINAL HEMORRHAGES

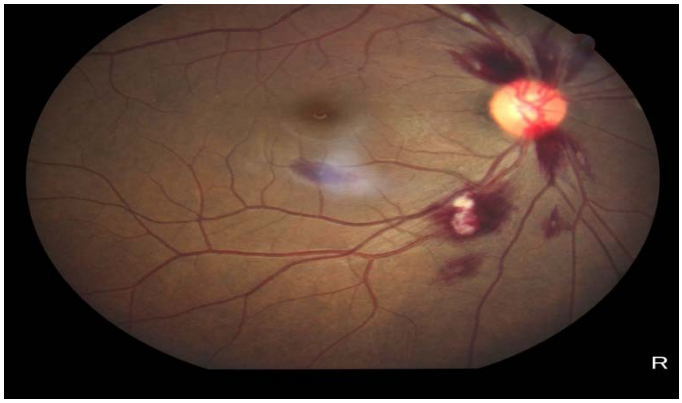


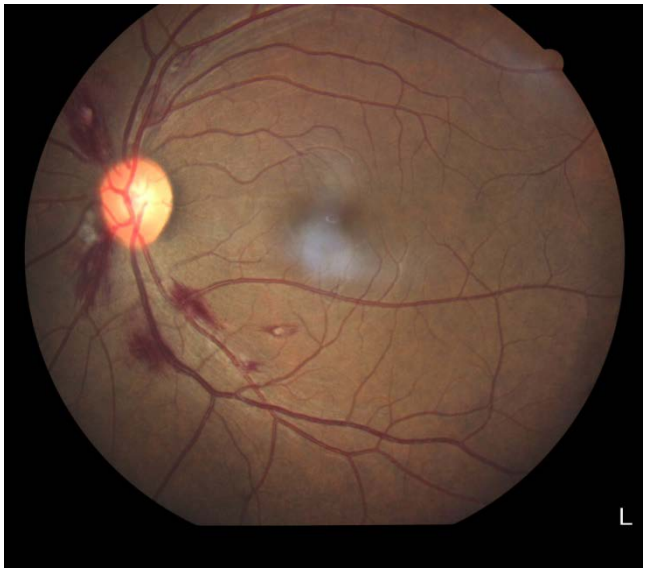
PRE – RETINAL HEMORRHAGE



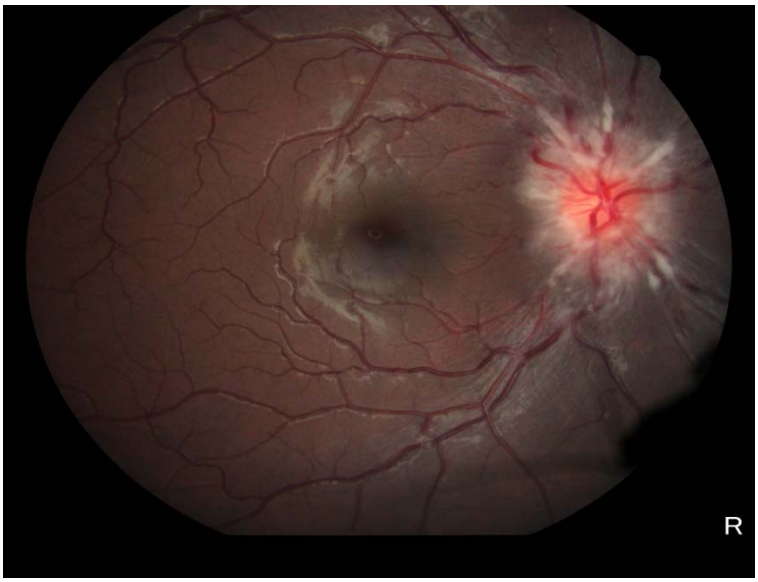


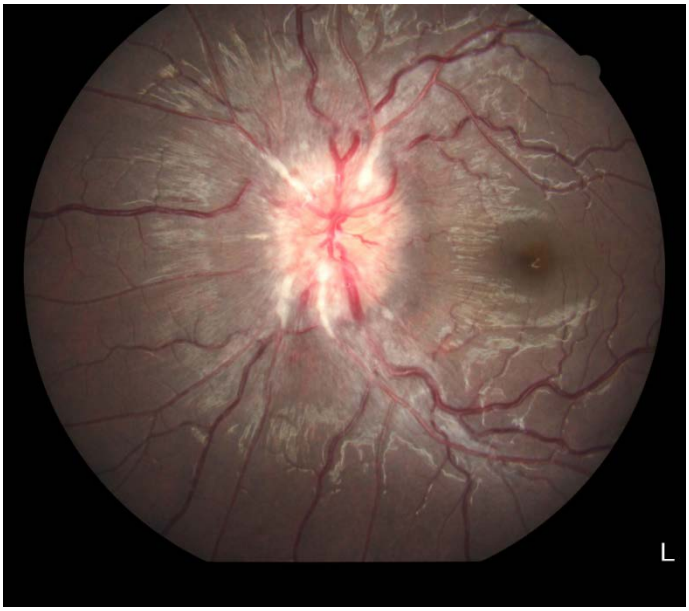
ROTH SPOTS



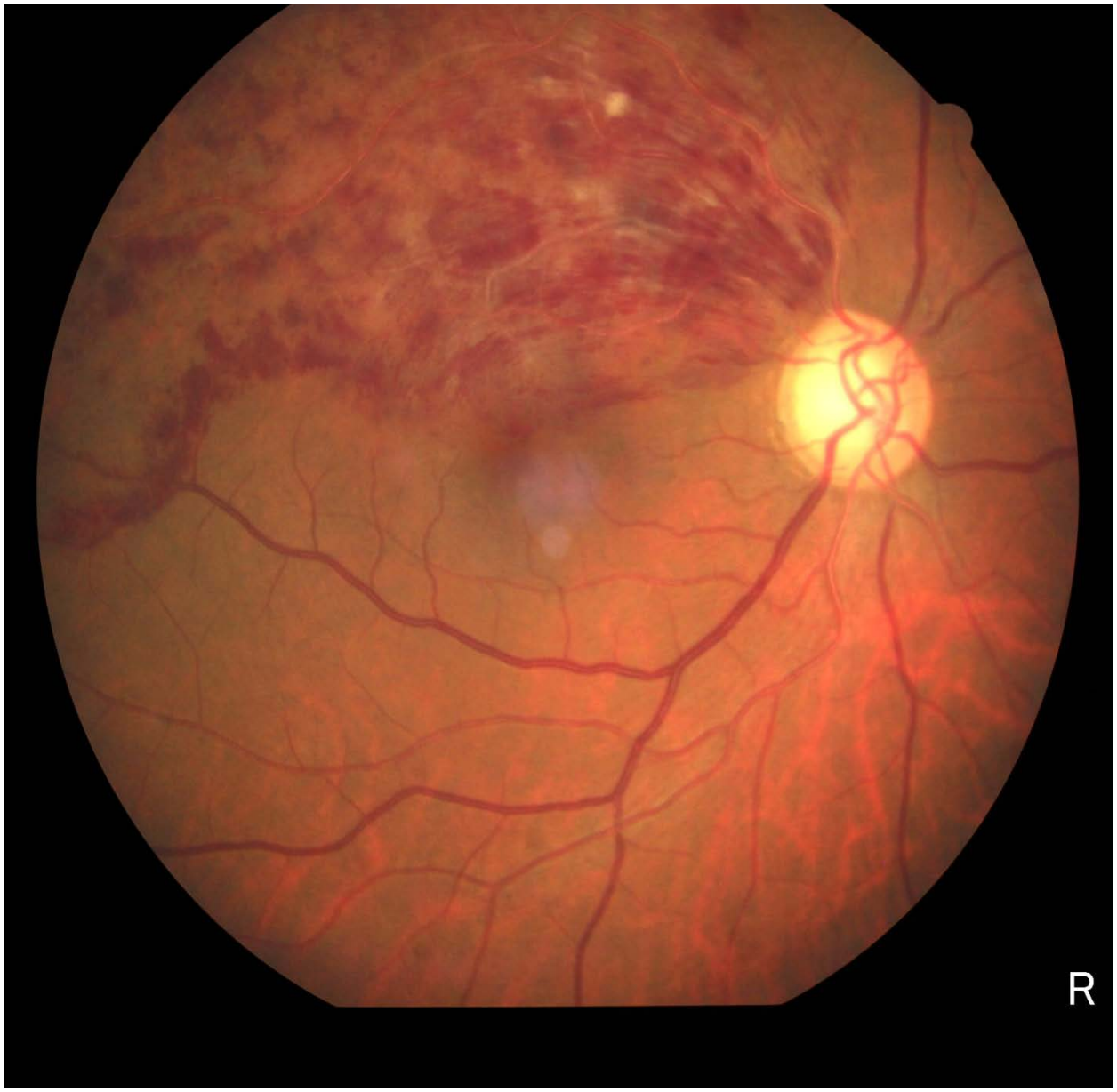


PAPILLOEDEMA



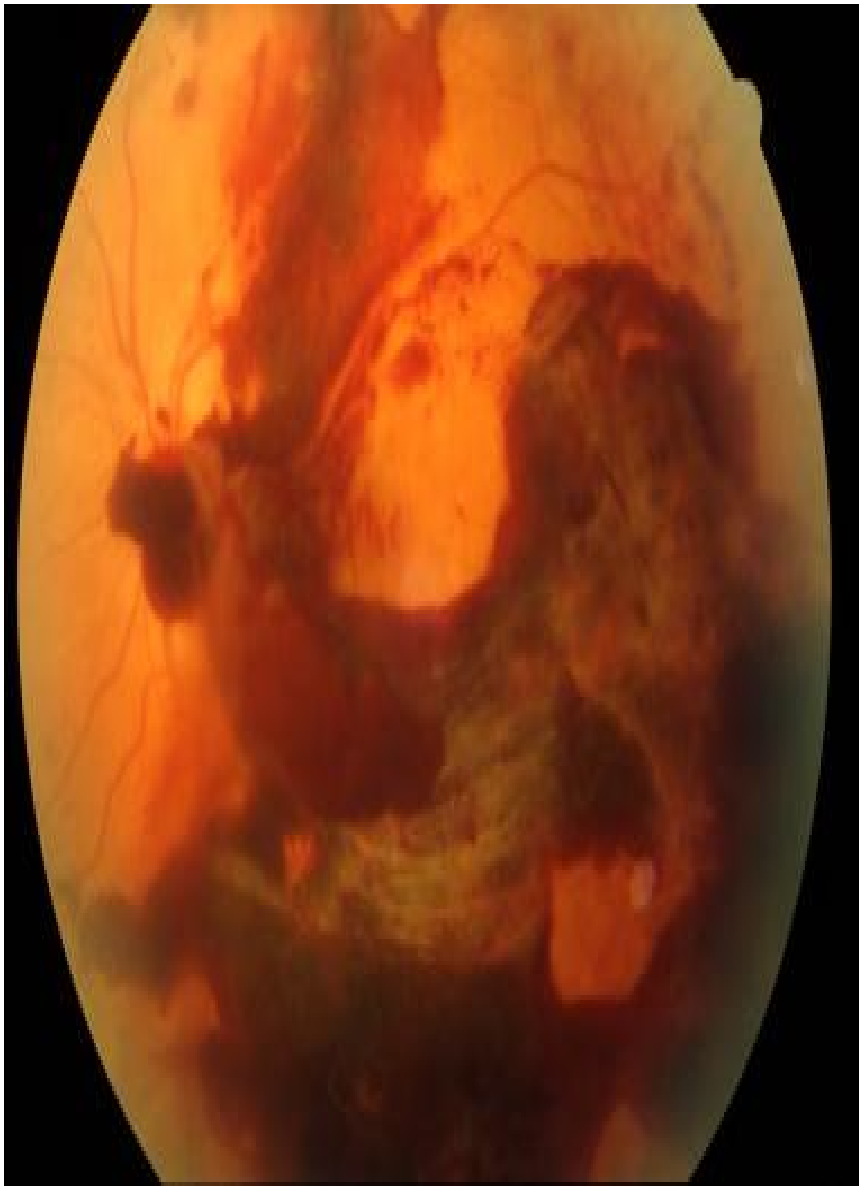


(RE) SUPERO TEMPORAL BRANCH RETINAL VEIN OCCLUSION



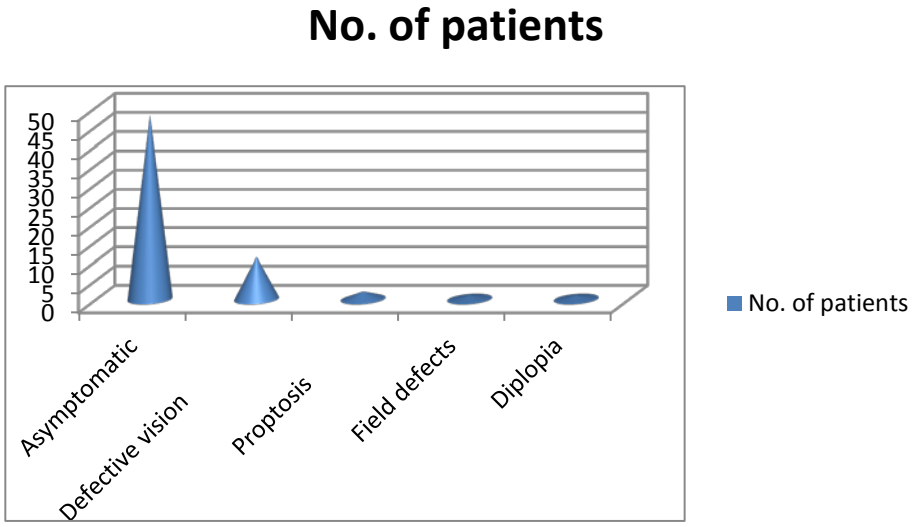
PROPTOSIS

VITREOUS HEMORRHAGE



4. **SYMPTOMS AT PRESENTATION:**

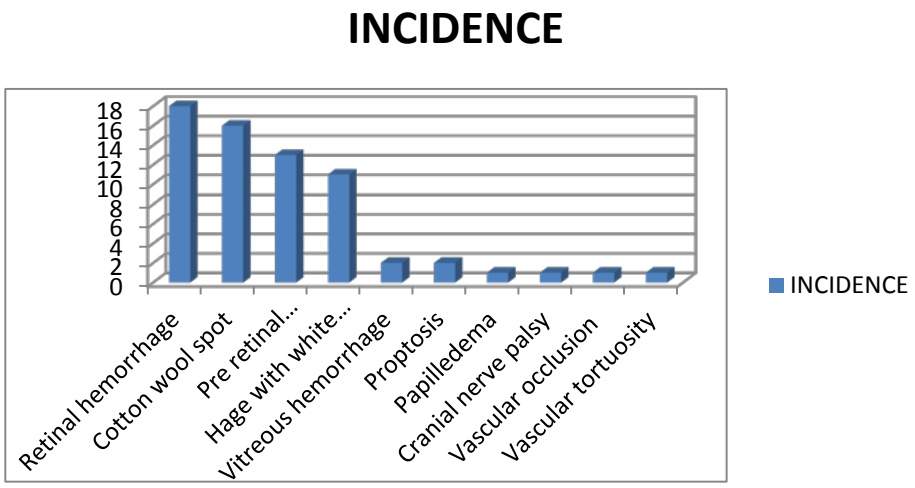
SYMPTOMS	NO.OF PATIENTS	PERCENTAGE
Asymptomatic	42	66%
Defective Vision	17	27%
Proptosis	2	3%
Field defects	1	2%
Diplopia	1	2%



Most patients had no ocular symptoms at presentation and 21 were symptomatic. 17 patients (27%) presented with defective vision. Two patients presented as proptosis and later were diagnosed as haematological malignancy.

5.OCULAR MANIFESTATIONS IN MALIGANT DISORDERS:

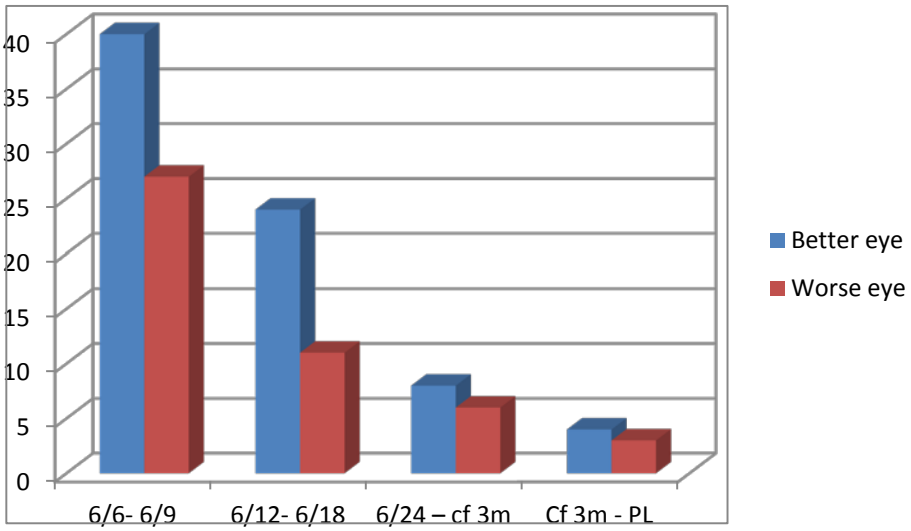
LESIONS	INCIDENCE	PERCENTAGE
Retinal hemorrhage	18	28%
Cotton wool spot	16	25%
Pre retinal hemorrhage	13	20%
Hage with white centre	11	17%
Vitreous hemorrhage	2	3%
Proptosis	2	3%
Papilledema	1	1.5%
Cranial nerve palsy	1	1.5%
Vascular occlusion	1	1.5%
Vascular tortuosity	1	1.5%



Retinal hemorrhages in the form of superficial hemorrhages were the most common finding followed by cotton wool spots and pre- retinal hemorrhages.

6.VISUAL ACUITY AT PRESENTATION

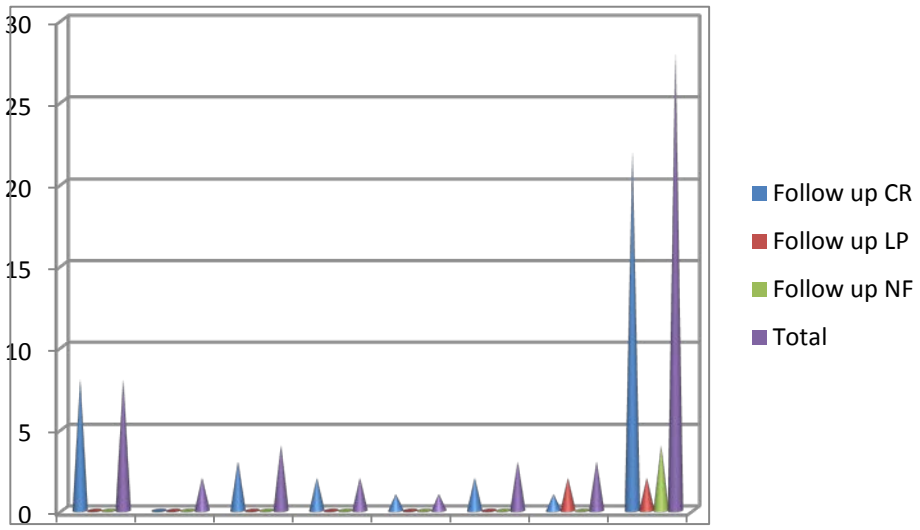
Vision	Better eye	Worse eye
6/6- 6/9	40 (63%)	27 (43%)
6/12- 6/18	24(3%)	11 (7%)
6/24 – cf 3m	8(16%)	6(11%)
Cf 3m – PL	4(14%)	3(6%)



Most patients presented with good vision at presentation, while 33 % had poor vision, commonly due to fundus changes including pre-retinal hemorrhages over the macula followed by vitreal haemorrhages.

7.RESOLUTION AND FOLLOW UP

		RESOLUTION AND FOLLOW UP							
		NHL	HL	AML	ALL	CML	CLL	MM	Total
Complete Resolution	CR	8	2	3	1	1	1	1	17
Lesion Persisted	LP	0	0	0	1	0	2	2	5
No follow Up	NF	0	0	1	0	0	0	0	1
Total		8	2	4	2	1	3	3	23



Resolution of lesions was noted in most patients (74%), while persistence of lesions was seen in 22 % of the cases.

RESULTS

NON MALIGNANT HEMATOLOGICAL DISORDERS:

Among 100 patients, 37 were observed to have non – malignant disease of the blood, most common of them was Iron deficiency anemia (38%) , concurrent with studies done by Quadri et al (34 %).

STUDY	COMMON INCIDENCE	AGE GROUP	OCULAR FEATURES
Lange et al	Anemia(37%)	25- 60	Pallor > Retinal hemorrhages (70%)
Holt J.M & Gordensmith	Anemia(49%)	40-60	Retinal hemorrhages(67%)
Rubenstein and Yanoff	Anemia(22%)	20- 50	Retinal hemorrhages(41%)
Merin S.& Freund	Anemia (30%) (Nutritional)	20 -40	Retinal hemorrhages(55%)
Our study	Anemia (38%) (Iron deficiency)	20 -40 (32%)	Pallor > Retinal hemorrhages(62%)

Our study showed comparable results with most other studies with non – malignant disorders of the blood most commonly were seen in the age group of 20 – 40 (32%) with male preponderance (65%). Iron deficiency anemia was most commonly seen among female while aplastic anemia were most common in men.

Visual acuity at presentation was good(6/6 to 6/18) in almost 70 % of the patients. 10 patients presented with defective vision, of whom 9 were attributed to pre- retinal haemorrhages over the macula and one to unilateral disc edema (0.3%) in one case of megaloblastic anemia.

These ten cases were diagnosed by the ophthalmologist as cases of haematological disorders and further evaluated and treated.

Conjunctival pallor (92%)was most common ocular manifestation followed by retinal haemorrhages (62%) . Similar findings were noted by Lange et al who reported 71% and Merin Freund et al (63%) retinal lesions.

Aplastic anemias demonstrated the maximum association with ocular findings (100%).

Of the 14 patients of Iron deficiency anemia, only one patient showed persistence of lesions. This was due to poor adherence to systemic treatment. The lesions in aplastic anemia, megaloblastic , haemolytic anemia and thalassemias showed resolution. One case of Anemia of chronic disease with underlying chronic renal failure showed persistence of lesions due to progression of the systemic disease.

Among thrombocytopenia, resolution was noted in one patient while the other patient with lesions died during the period of follow up due to systemic complications. Retinal lesions persisted in one patient who was under treatment but this was not statistically significant due to small sample size.

MALIGNANT HEMATOLOGICAL DISORDERS:

Among 100 patients enrolled in our study, 63 patients had malignant disorders of the blood , including Non –Hodgkin Lymphoma (46%), being the most common , followed by Chronic leukemias , acute leukemias and paraproteinemias.

Comparison of incidence of ocular involvement (mostly metastasis and infiltrations) in patients with hematological malignancies in different studies :

INVESTIGATOR	INCIDENCE
Allen and Straatsma(1961)	38 of 76(50%)
Robb,Ervin et al(1979)	30-44 of 60(50-73%)
Kincaid and Green(1983)	284 of 357(50%)
Nelson et al(1983)	33 of 117(28%)
Schachat et al (1989)	51 of 120(42%)
Leonardy et al (1990)	42 of 135(31%)
Our study	23 of 63(37%)

The malignancies of blood were more prevalent in the age group of 20- 40 years (32%) as in studies done by Nelson et al and Leonardy et al.

Majority of the patients were male 38 (60%) as compared to 25 females, possibly due to the increased incidence of haematological malignancies in males.

Among 63 patients, 21 patients (33%) presented first to the Department of Ophthalmology with complaints of Defective vision in 17 patients (33%), Proptosis in two cases(3%) one in a case of AML and the other in a case of Multiple myeloma. Proptosis was found to be caused by tumour infiltration into the orbit on imaging.

One case of multiple myeloma presented with defective vision and further was due to Branch Retinal Vein Occlusion, most likely secondary to hyperviscosity. Defective vision was noted due to pre-retinal haemorrhages, retinal and vitreous hemorrhage ,and in few cases due orbital infiltration. Shirley Fung et al reported in a study that among 8 patients with multiple myeloma, 1 had retinopathy due to hyperviscosity while 3 others had orbital involvement.

Among the 63 cases, 23(35%) had ocular manifestations of which 4 were in the anterior segment and 20 in the posterior segment. Retinal haemorrhages were the most manifestations (28%) followed by soft exudates (25%) as also reported in study by Holt JM& Gordensmith et al.

One case of multiple myeloma presented with 6^{th} nerve palsy and papilledema, due to CNS infiltration. A similar case was reported in a study by Osama Baddeb et al showing cranial nerve palsy secondary to CNS involvement. While one case of NHL presented with acute painless vision loss, due to vitreous hemorrhage.

13 of the 23 showed lesions at presentation showed complete resolution after initiation of chemotherapy and consequent improvement in the blood picture. The rate of

improvement was inversely associated to the severity of the disease at the time of presentation.

Retinal lesions resolved over about 2 to 6 months. Cotton wool spots were earliest to resolve followed by superficial hemorrhages. Intraretinal and vitreous hemorrhages took the longest time for resolution. 6 of the 21 patients were lost to follow up.

29 cases of Non – Hodgkin's lymphoma were included in the study which over 6 months showed resolution in all of the 8 patients who demonstrated lesions at presentation and had statistical significance (p value <0.0001).

In acute leukemias, of the total 11 cases, 6 showed lesions at presentation. In cases of AML, 4 of the six patients on treatment, 3 showed complete resolution. In 2 cases of ALL, lesions persisted in one patient due to incomplete treatment.

Chronic leukemias showed lesions only in 4 patients. 2 of 3 cases of CLL showed resolution with one patient lost to follow-up due to death. (p value 0.0143)

6 cases of Multiple myeloma were recruited in the study, three showed lesions of who only one had complete resolution. Lesions persisted in 2 patients due to incomplete treatment and relapse in the other.

CONCLUSION:

- In this study, malignant disorders were more than non- malignant diseases.
- Both disorders showed male preponderance with most diseases, while iron-deficiency anemia was more common in females.
- Most common age group was 20-40 years.
- Iron- deficiency anemia was the most common non-malignant disorder and Non Hodgkins Lymphoma was the most common malignant condition in our study.
- Aplastic anemia showed strong association with ocular lesions with almost all patients showing retinopathy.
- 31 patients presented primarily to the ophthalmologist with defective vision as the most common symptom and following evaluation were diagnosed to have blood dyscrasias, thus emphasizing the need for thorough ocular screening.
- Pallor was the most common sign in the anemia. Most common ocular manifestations among haematological disorders was retinal haemorrhages, followed by cotton-wool spots indicating retinal ischemia.
- Ocular lesions showed rapid resolution with treatment except in cases of incomplete treatment in non- malignant disorders. Ocular manifestations persisted in malignant diseases due to relapse of the underlying disease.
- Ocular manifestations are a frequent occurrence in blood dyscrasias and should be evaluated with a high index of suspicion when found.

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PROFOMA

Serial no:

Name :

Age:

Sex:

Occupation:

Address :

Ocular complaints:

Associated Systemic illness :

Family history :

OCULAR EXAMINATION

	RE	**LE**
Vision		
Eyelids and lashes		
Extra ocular movements		
Slit lamp examination		
Conjunctiva		
Cornea		
Anterior chamber		

Iris

Pupil

Lens

IOP

Colour vision:

Fields :

Amsler Grid:

Fundus :

90 D slit lamp:

IDO:

Fluorescein Angiography:

Date: Reactions(if any):

Dye used:

DIAGNOSIS:

PATHOLOGICAL DIAGNOSIS:

LABORATORY DIAGNOSIS:

IMPRESSION:

ADVICE:

கண்ணியல்துறை, அரசு ஸ்டான்லி மருத்துவக்கல்லூரி, சென்னை – 600 001

தகவல் படிவம்

தலைப்பு : இரத்த நோய்களில் வரும் கண் குறைபாடுகள் பற்றிய ஓர் ஆய்வு

ஸ்டான்லி மருத்துவக் கல்லூரியில் கண்ணியல் துறை முதுகலை பட்ட மேற்படிப்பு படிக்கும் மருத்துவ மாணவியாகிய நான் (டாக்டர் S. சுஹாசினி) மேலே குறிப்பிட்ட தலைப்பில் ஆய்வு செய்யப்போகிறேன்.

கண் நரம்பு சற்றே பாதிக்கப்பட்ட நோயாளியான உங்கள் கண்களை பரிசோதனை செய்ய சம்மதம் கேட்கிறேன். நீங்கள் சம்மதம் தெரிவித்தால் உங்களின் கண்களை பரிசோதனை செய்வேன் நீங்கள் இதில் பங்கேற்பதன் மூலம் உங்கள் விழித்திரை மற்றும் கண் நரம்பு பாதிப்புகள் உள்ளதா, ஏற்படும் பாதிப்புகள் எந்த அளவு உள்ளது என அறிவதற்கு உதவும்.

இந்த ஆய்வில் விழித்திரை மற்றும் கண் நரம்பு எந்த அளவு பாதிக்கப்பட்டுள்ளது. என்பதை மட்டுமே பரிசோதிக்கப் போகிறேன். இவ் ஆய்வில் பங்கேற்பவர்களுக்கு எவ்வித ஊசியோ பங்கேற்பவர்கள் பாதிக்கப்படும் பரிசோதனையே (Invasive diagnostic test) செய்யப்படமாட்டாது என உறுதியளிக்கிறேன். இவ் ஆய்வில் கலந்து கொள்பவரின் பெயரும், நோயும், ரகசியமாக வைக்கப்படும் என்றும் உறுதியளிக்கிறேன். பங்கேற்பாளர் எந்த நேரமும் எந்த சட்ட சிக்கல்களுக்கும் உட்படாமல் இவ்வாய்விலிருந்து விலகிக் கொள்ளலாம், தேவையற்ற எந்த கேள்விகளும் கேட்கப்படமாட்டாது. தேவையற்ற எந்த பரிசோதனையும் செய்யப்படமாட்டாது என்று உதியளிக்கிறேன்.

உங்களுடைய பங்கேற்பு முழுவதும் உங்களுடைய விருப்பத்தைச் சார்ந்தது. இதில் நீங்கள் பங்கேற்க மறுக்கவோ, பாதியில் வெளியேறிவிடவோ அல்லது குறிப்பிட்ட கேள்விகளுக்கு பதிலளிக்க மறுக்கவோ உங்களுக்கு உரிமை உண்டு.

தாங்கள் இது பற்றி வேறு விபரங்கள் தெரிய விரும்பினால் என்னிடம் இது பற்றி கேட்டு தெரிந்து கொள்ளலாம்.

டாக்டர் S. சுஹாசினி
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செல் : 9884030779

ஆய்வாளரின் பெயர் மற்றும் கையொப்பம் நாள் :

Sunl

கண்ணியல்துறை, அரசு ஸ்டான்லி மருத்துவக்கல்லூரி, சென்னை – 600 001

ஒப்புதல் படிவம்

தலைப்பு : இரத்த நோய்களில் வரும் கண் குறைபாடுகள் பற்றிய ஓர் ஆய்வு

பங்கு பெறுபவரின் பெயர் :
பங்கு பெறுவோரின் எண் :

மேலே குறிப்பிட்ட ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது.

இதில் மருத்துவர் என் மீது எந்த ஊசியோ (Invasive diagnostic test) செய்யப்போவதில்லை என அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ, இதைச் சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும், இவ் ஆய்வில் பங்குபெறும் மருத்துவர் என் மருத்துவ அறிக்கைகளை பார்க்க என் அனுமதி தேவையில்லை. இதன் மூலம் கிடைக்கும் தகவல்களையும் பரிசோதனை முடிவுகளையும் பார்ப்பதற்கும், பயன் படுத்துவதற்கும் முழு மனதுடன் சம்மதிக்கிறேன்.

எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வேன். எதிர்பாராத வழக்கத்திற்கு மாறான நோய் அறிகுறி தென்பட்டால் அதை மருத்துவரிடம் தெரிவிப்பேன்.

இந்த ஆய்வில் நான் தன்னிச்சையாக தான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ, எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ் ஆய்வில் இருந்து விலகிக் கொள்ளலாம் என்று அறிந்து கொண்டேன்.

இந்த ஆய்வின் எனக்கு தேவையான அனைத்து பரிசோதனையும் செய்து கொள்ள முழு மனதுடன் சம்மதிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம்

கட்ட விரல் ரேகை

நாள் :

நான் இவ்ஆய்வைப் பற்றி அனைத்து விபரங்களையும் மேற்குறிப்பிட்ட நபர் புரிந்து கொள்ளும்படி அவருக்கு தெரிந்த மொழியில் எடுத்துக்கூறி சம்மதம் பெற்றுள்ளேன்.

ஆய்வாளரின் பெயர் மற்றும் கையொப்பம்.

நாள் :

Sunl

KEY TO MASTER CHART

ADNEXAL	PROPTOSIS		A
	LID SWELLING		B
ANTERIOR	TORTUOUS CONJ VESSELS		C
	SCH		D
	HEMORRHAGES		
POSTERIOR		PRE RETINAL	E1
		RETINAL VITREOUS HAGE WITH WHITE CENTRE	E2 E3 E4
	CWS		F
	HARD EXUDATE		G
	VASCULAR TORT VASC		H
	OCCLUSION		I
	VITRITIS		J
	VIT HAGE		K
	PAPILLEDEMA		L
	CRANIAL NERVE PALSY		M
	DISC EDEMA		N
	COMPLETE RESOLUTION		
LP	PERSISTANCE OF LESIONS		
NF	NO FOLLOW UP		

CT	COMPLETE TREATMENT
UT	UNDER TREATMENT
REL	RELAPSE
R	REMISSION
NF	NO FOLLOW UP
IT	INCOMPLETE TREATMENT

M MALE	
F FEMALE	
6/6 – 6/9	1
6/12- 6/18	2
6/24 – 3M CF	3
3M CF – NIL	
PL	4

IDA IRON DEFICIENCY ANEMIA

AA APLASTIC ANEMIA

HA HEMOLYTIC ANEMIA

MAMEGALOBLASTIC ANEMIA

ACD ANEMIA OF CHRONIC DISEASE

THAL THALASEMIA

TP THROMBOCYTOPENIA

HL HODGKIN LYMPHOMA

NHL NON HODGKIN LYMPHOMA

AML ACUTE MYELOID LEUKEMIA

ALL ACUTE LYMPHOCYTIC LEUKEMIA

CML CHRONIC MYELOID LEUKEMIA

CLL CHRONIC LYMPHOCYTIC LEUKEMIA

MM MULTIPLE MYELOMA

Name	age	Sex	Diagnosis	RE vn	LE vn	RE	LE	COURSE	FOLLOW UP
Rajeshwari	18	F	IDA	3	2	E2,F	E2D	CT	CR
Latha	32	F	IDA	1	2	E2,D	E1,E2,F	CT	CR
Parvathi	37	F	IDA	1	1	E2	E4,D	CT	CR
Shiva kumar	71	M	IDA	1	1			CT	
Jemmy	26	F	IDA	1	3	E4,D	E2,F	CT	CR
Santhy	17	F	IDA	1	1	E2	E2	NF	NF
Marriyappan	65	M	IDA	1	1	E2,F	E2,F	CT	CR
Ambiga	22	F	IDA	1	3		E1,F	CT	CR
Aruna	29	F	IDA	3	1	E2	E4	CT	CR
Radha	37	F	IDA	1	3	E4,F	E1	CT	CR
Maheshwari	26	F	IDA	2	1	E2,F	E2	CT	LP
Sujatha	43	F	IDA	1	2		E4	CT	CR
Sudhakar	79	M	IDA	2	1			CT	
Viji	57	F	IDA	1	1		E1	CT	CR
Kamalhasan	19	M	AA	3	3	E2,F	E1,F	UT	CR
Kalaiarasan	48	M	AA	1	2	D	E2,D	UT	CR
Arumugam	28	M	AA	1	3	E2,F	E4,F	UT	CR
Srinath	33	M	AA	1	2		E1,D	UT	CR
Selvakumar	49	M	AA	2	1	E2,F	E1,F	NF	NF
Eshwaran	12	M	AA	2	1	E1	E1,D	UT	CR
Tamilvannan	52	M	AA	1	1	E2	E2,F	NF	NF
Saravanan	51	M	AA	2	1		E2	UT	CR
Chinamalai	46	M	MA	1	1			CT	
Palanisamy	27	M	MA	2	1	E2,F	E4,F	CT	
Shanharalingam	31	M	MA	1	2	E1	E2,F	CT	CR
Vadivelu	39	M	MA	1	1			CT	
Nagarajan	14	M	MA	2	1			CT	
Kmamakannan	54	M	HA	1	1			CT	
Mohamed	22	M	HA	2	1	E1,F	E1,E2,F	CT	CR
Anandan	57	M	HA	1	2			UT	
Ashwin	19	M	HA	1	3			UT	
Abdulla	72	M	ACD	1	2			UT	
Arokiyam	64	F	ACD	3	1	E2	D	REL	LP
Raja	12	M	THAL	1	1		E2	UT	CR
Asha	26	F	TP	1	1			R	
Raman	43	M	TP	1	1	E1,F	E2,F	R	CR
Kandan	68	M	TP	1	1	E3,F	E2,F	UT	LP
Kanagavalli	50	F	AML	2	1	E4	E2,F	R	CR
Kalavathi	15	F	AML	hm	cf cf		E2, L ,M	NF	NF
Raman	19	M	AML	1	1	E1,F	E2,F	R	CR
Deepan	22	M	AML	1	1			R	

Devakar	48	M	AML	2	1	E2,F	E4	R	CR
Bharathi	11	M	AML	3	1			R	
Biravi	7	F	ALL	1	1			R	
Jayalakshmi	13	F	ALL	1	2	E4	E2,E4	IT	LP
Sathish	31	M	ALL	1	3	E2,F	E4	IT	CR
Sevaraj	28	M	ALL	2	3			R	
Prasanna	19	M	ALL	1	1			R	
Bhagya	73	F	CLL	2	1			R	
Muthkumar	53	M	CLL	1	1			R	
Murali	10	M	CLL	3	1	E2,F	E4,F	R	CR
Murugan	21	M	CLL	1	2		E4,F	R	CR
Malarvizhi	64	F	CLL	1	1			R	
Ramesh	43	M	CLL	1	3			R	
Balasubran	19	M	CLL	1	2	E4,F	E2,E4	NF	NF
Ahmed	45	M	CML	2	2			R	
Varalakshmi	53	F	CML	1	1			R	
Amalraj	31	M	CML	2	3			R	
Radha	62	M	CML	1	3	E2,F	E2,E4,F	R	CR
Divya	39	F	CML	1	1			R	
Shivakumar	67	M	MM	1	1			R	
Arumugam	52	M	MM	1	1		A	R	CR
Ramayee	85	F	MM	1	3		I,H,F	REL	LP
Ganapathy	71	M	MM	3	1			R	
kannagi	61	M	MM	1	1	E2	E4,F	R	LP
Venila	58	F	MM	1	1			R	
Murugan	32	M	HL	1	1	E2,F	E4,F	NF	NF
Mohini	41	F	HL	3	1			R	
Rajesh	38	M	HL	1	1			R	
Sampath	32	M	HL	1	3			R	
Vel	44	M	HL	1	1	E3,F	E2,F	NF	NF
Rajan	58	M	NHL	1	1			R	
Subramaniyam	23	M	NHL	1	1			R	
Suresh	28	M	NHL	1	3	E1,F	E2,F	NF	NF
Kokila	55	F	NHL	1	1			R	
Bharath	57	M	NHL	1	1			R	
Prashanth	16	M	NHL	3	1			R	
Aradhana	7	F	NHL	1	1	E4,F	E2	R	CR
Gautham	14	M	NHL	1	1			R	
Priya	21	F	NHL	1	1			R	
Raju	76	M	NHL	1	1			R	
Kumar	69	M	NHL	1	1			R	
Selvam	33	M	NHL	3	1			R	
Prabhakar	44	M	NHL	1	1	E2,F	E2,F	NF	NF

Shanthi	50	F	NHL	1	1			R	
Selvi	37	F	NHL	4PL	1	K		R	
Priyanka	19	F	NHL	1	1			R	
Sathish	10	M	NHL	1	1		A	R	CR
Nagarajan	34	M	NHL	1	1			R	
Pooja	17	F	NHL	1	1			R	
Anandan	9	M	NHL	1	3			R	
Ravichandran	12	M	NHL	1	1	E1	E2	REL	CR
Kalaiselvi	39	F	NHL	1	1			R	
Sakthivel	32	M	NHL	1	1			R	
Sundaram	37	M	NHL	1	1			R	
Kuppammal	80	F	NHL	1	1			R	
Eshwaran	46	M	NHL	1	1	E2	B	R	CR
Mohan	51	M	NHL	3	1			R	
Meiyappan	22	M	NHL	1	1	E4,F	E2,E3,F	R	CR
Manoharan	14	M	NHL	1	1			R	