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Immunohistochemistry of Kikuchi Fugimoto Disease

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Abstract

Background

Kikuchi Fujimoto Disease (KFD) Is A Self Limiting Sub Acute Necrotizing Regional Lymphadenopathy Associated With Mild Fever. It Is More Common In Young Females Of Asian Origin. KFD Has To Be Differentiated From Other Necrotizing Lymphadenopathies Such As Tuberculosis, Lupus Erythematosus, And Some Lymphomas, Since Their Course And Treatment Are Entirely Different. Hence, This Study Intends To Delineate The Immunohistochemical Profile Of Kikuchi Fujimoto Disease In Order To Aid In Differentiating It From Others.

Aim

To Describe The Presence Or Absence Of Different Histomorphological Features And Immunohistochemical Markers In Relation To The Topography Of The Nodes In The Different Histological Subsets Of The Disease

Material and Methods

25 Cases Of Kikuchi Fugimoto Disease, Diagnosed By Histopathological Features, Were Selected. The Clinical Details And Histopathological Features, Including Presence Of Architectural Effacement Of Lymph Node, Follicular Hyperplasia, Paracortical Hyperplasia, Proliferation Centres, Geographic Necrosis, Apoptosis And Foam Cells, Were Analysed. Immunohistochemistry (IHC) Was Done In All 25 Cases And Expression Of 10 IHC Markers In The Cells Were Noted And Analysed.

Results and Conclusions

Diagnosis Of Kikuchi-Fujimoto Disease Largely Relies On The Histomorphological Features, Especially The Presence Of Necrosis And Apoptotic Debris With Plenty Of Histiocytes And Almost Complete Absence Of Neutrophils And Eosinophils. Cytoplasmic MPO Positivity In Histiocytes Is Helpful In Differentiating Kikuchi-Fujimoto Disease From Other Necrotizing Lymphadenitis And Lymphoma, Although It Cannot Differentiate It From Lupus Lymphadenitis. CD30 Expression Is Typically Absent Within Histiocytes In Kikuchi-Fujimoto Disease, Which Can Differentiate The Above From Several Lymphomas.

Keywords

Immunohistochemistry Of Kikuchi Disease; Kikuchi Disease; Kikuchi Fujimoto Disease

Introduction

Kikuchi Disease Also Known As Kikuchi Fujimoto Disease (KFD) Or Histiocytic Necrotizing Lymphadenitis Is A Sub Acute Necrotizing Regional Lymphadenopathy Associated With Mild Fever. It Is More Common In

Young Of Asian Origin And Show A Slight Female Preponderance. The Etiology And Pathogenesis Still Remain A Mystery. Infectious And Autoimmune Causes Have Been Proposed.[1, 2]

KFD Is Diagnosed On The Basis Of Microscopic Evaluation Of Affected Lymph Nodes. No Radiographic Or Serological Marker Is Helpful In Diagnosing KFD.

The Histomorphology Is Characterized By Necrosis With Marked Karyorrhexis And A Significant Absence Of Granulocytes.

Kikuchi Disease Is A Self Limiting Disease. It Is Important To Include It In The Differential Diagnosis Of Other Necrotizing Lymphadenopathies Such As Tuberculosis, Lupus Erythematosus, Or Some Lymphomas, Since Their Course And Treatment Are Entirely Different. Hence, This Study Intends To Delineate The Immunohistochemical Profile Of The Disease In Order To Aid In Differentiating It From Others.

Materials & Methods

Design of Study- Descriptive Study

Inclusion Criteria

All Cases Of Kikuchi – Fujimoto Disease Diagnosed By Lymph Node Biopsy During The Period January 2010 To August 2015 In The Department Of Pathology, Government Medical College, Kozhikode.

Methods

Clinical Data: Collected From The Case Sheets And Histopathology Requisition Forms. The Diagnosis Was Made On Haematoxylin &Eosin Sections And Representative Tissue Blocks Were Selected For Immunohistochemistry.

H&E Morphology

Blocks Of The Lymph Node Biopsies Were Sectioned And Stained With Hematoxylin And Eosin. The Following Parameters Were Noted

1. **Architecture Of Lymph Node:** Whether Total Or Partial Effacement Of Architecture
2. **Follicular Hyperplasia:** Whether Present Or Absent
3. **Paracortical Hyperplasia:** Considered To Be Present If A Starry Sky Pattern Present In The Paracortex Due To Histiocytes And Plasmacytoid Lymphocytes- Present /Absent
4. **Proliferation Centres:** Light Staining Areas In Which Transformed Cells And Macrophages Are The Predominant Cells- Present /Absent
5. **Geographic Necrosis:** Bland Eosinophilic Areas Of Widespread Cell Death- Present /Absent
6. Apoptosis: Within The Proliferation Centres- Present /Absent
7. **Foam Cells:** Whether Scattered Or Seen In Clusters.

The Cases Were Then Classified Into The Following Categories Of Kikuchi Disease.

1. **Proliferative Type (Pt):** If Proliferative Centres Predominate And Necrotic Areas Are Less Than 10% Of The Total.
2. **Necrotic Type (Nt):** Area Of Geographic Necrosis Is More Than 10% Of The Total.
3. **Xanthomatous Type (Xt):** Foam Cell Collections Account For More Area Than Proliferation Centres Or Necrosis.

After Confirmation Of Diagnosis And Classification Of Kikuchi Disease, Representative Blocks Were Selected For Doing The Following Immunohistochemical Markers.

Immunohistochemistry (IHC)

Staining Protocol In Brief

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Cut 3mm Sections On Charged Slides And Incubate At 60-70^{o}c For 1 Hour. Sections Are Deparaffinized In Xylene And Hydrated Through Descending Grades Of Alcohol. Wash In Distilled Water And Place Sections In Tris EDTA Borate Buffer For Antigen Retrieval By Heat Method In Multiepitope Antigen Retrieval System (MERS) Followed By Cooling To Room Temperature. Endogenous Peroxidase Is Abolished By Submerging The Slides In Quenching Solution (30 Ml 30% H2O2: 300 Ml Distilled Water) For 5 Minutes And Then Washed In Wash Buffer. Sections Are Dried By Wiping All Around. Serum Blocking Solution Is Added For 10 Minutes. After This The Sections Are Blotted And Primary Antibody Added On To The Sections And Kept For 30 Minutes In A Moisture Chamber; Washed In Buffer Twice For 2 Minutes Each. Polyexcel Target Binder Reagent Is Added And Kept For 15 Minutes And Washed With Buffer Twice For 2 Minutes Each. Polyexcel HRP Is Added And Kept For 15 Minutes And Washed With Buffer Twice For 2 Minutes Each. The Chromogen Diaminobenzidine (DAB) Is Added For 5 Minutes; Washed In Distilled Water And Then Counterstained With Hematoxylin For 30 Seconds And Washed In Water. The Sections Are Then Dehydrated; Cleared And Mounted. The Antibodies Used For IHC Were CD3, CD4, CD8, CD20, CD30, CD15, CD56, EMA, MPO, And Ki67. The Presence Or Absence Of Positivity And Its Abundance If Positive, Will Be Noted In Terms Of The Topography Of The Node And The Different Patterns Seen In The Node.

Observations & Results

25 Cases Of Kikuchi Fujimoto Disease, Diagnosed In The Department Of Pathology, Govt. Medical College, Kozhikode, Were Studied.

Clinical Features

The Age Of Patients In The Study Ranged From 8 To 45 Years. The Mean Age Was 26.4 Years. The Female- Male Ratio Was

4. The Age And Sex Distribution Of Cases Are Shown In Figure

1.The Main Symptom Of Patients Was Cervical Lymph Node Enlargement (22/25).The Axillary Lymph Nodes Were Involved In 2 Patients. Only 2 Patients Had A Generalized Lymph Node Enlargement. Other Symptoms Noted Were Fever In 11 Patients, Hepatosplenomegaly In 2 Patients And Pancytopenia In 1 Patient (Figure 2). More Than Two Thirds Of The Cases Had Lymphadenopathy Lasting For 2-3 Weeks Duration. SLE Was Ruled Out In All Patients By Serology.

Histopathology

The Lymph Node In Kikuchi-Fujimoto Disease Showed A Mixture Of Different Histological Patterns (Figure.3). 20% Cases Showed Complete Effacement Of Lymph Node Architecture While Rest Showed Partial Effacement Only (Figure.7A). Retained Follicles Were Seen In Most Of The Cases But Follicular Hyperplasia Was Present Only In 5 Cases (20%) (Figure.7C). Widened Paracortex Was A Feature In Most Cases With 40% Cases Showing A Characteristic Starry Sky Pattern. The Proliferation Centres Were Light Staining Areas Seen Within The Paracortex As Seen In Figure.7C. The Light Staining Areas Showed A Mixture Of Lymphocytes, Immunoblasts And Histiocytes. Different Types Of Histiocytes Were Identified Including Epitheloid Histiocytes, Tingible Body Macrophages, Crescentic And Foamy Histiocytes. Apoptotic Debris Was The Characteristic Finding In Almost All Cases (Figure.7B). There Was Varying Degrees Of Apoptosis; Ranging From Focal To Uniformly Sprinkled Areas In Some And More

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Widespread In Others Resembling Areas Of Geographic Necrosis. Geographical Necrosis Varied From Small Foci To Large Patches Almost Replacing The Entire Node (Figure.7A). Neutrophils And Eosinophils Were Characteristically Absent And Plasma Cells Were Scarce. Foam Cells Were Not Seen In Significant Numbers.

Histological Subtypes

Of The 25 Cases, 14 Were Of Necrotic Type (56%) And 11 Were Of Proliferative Type (44%) . No Cases Were Identified As Xanthomatous Type (Figure 4)

Immunohistochemistry (IHC)

Immunohistochemistry Was Done With 10 Markers And The Results Were Noted As Positive Or Negative In The Three Cell Components- Histiocytes, Immunoblasts And Plasmacytoid Monocytes .The Positive Results Were Then Graded As Percentage Of Cells Showing Positivity And The Pattern Of Positivity -Nuclear, Cytoplasmic, Diffuse, Granular And Membranous, Were Also Recorded (Tables1&2; Figures 5&6).

CD 3 And CD 20, The Markers For T And B Lymphocyte Lineage Showed Their Normal Pattern Of Predominant Expression In Paracortex And Follicles Respectively. CD20 Expression Highlighted The Paracortical Widening. No Abnormal CD20 Expression Was Noted In The Paracortex. Within The Lesions, Lymphoid Cells Were Mainly Of T-Cell Phenotype, As Revealed By Their CD3 Expression. Most T Lymphocytes Carried The CD8 Molecule In Contrast To The CD4 Positive Cells In Normal (Figures.8A, B,C & D).

The Majority (90%) Of The CD3 Positive Immunoblasts Showed CD8 Positivity (Figure.7D). No Cases Showed CD20 Positivity Of Immunoblasts. These Findings Did Not Differ Significantly Between The Proliferative And Necrotizing Subgroups. The Only Difference Observed Was A Slightly Higher Content Of CD3+T Lymphocytes In The Proliferative Form.

60% Of The Cases Showed Strong MPO Positivity In The Cytoplasm Of 50-80%Histiocytes (Figure 9A). Other Cases Were MPO Negative Probably Because Of The Geographic Necrosis Involving Them. 44% Of The Cases Showed A Membranous EMA Positivity In The Histiocytes Ranging From 30-60% (11/25 Cases) (Figure.9B).

The Marker Of Interest In This Study Was CD30. CD30 Expression Was Seen Only In 6 Cases (24%) And Was Observed Only In The Immunoblasts (Figure 9C). CD30 Positivity Was Seen In Approximately 30-40% Of The Immunoblasts. The Histiocyte And Plasmacytoid Monocytes Were Negative For The Same (Figure 9D). The Immunoblasts Were Positive For CD3 (20 Cases), CD8 (19 Cases), CD30 (6 Cases). All The Cases Were Consistently Negative For CD56 And CD15.

The Proliferation Index (Ki67) In The Areas With Large Number Of Histiocytes And Apoptotic Debris Ranged From 3-20%. Ki67 Expression Was Predominantly Seen In Lymphoid Cells. Histiocytes Were Totally Negative For The Same. No Differences In Terms Of CD30, Ki-67 Or CD8 Expression Were Found Between The Two Histological Subtypes.

Discussion

In Our Study, The Age Group Of Patients Ranged From 8 Years To 45 Years. The Mean Age Was 26.4 Years. According To A Study Of 61 Case Of KFD By Lin HC Et Al[3], The Mean Age Is 21 Years. The Female To Male Ratio Obtained In Our Study Was 4 And Is In Accordance To The Study Conducted By Dorfman & Berry.[4]

The Main Clinical Symptom Was Non Tender Lymph Node Enlargement With 88% Involving The Cervical Region Followed By The Axillary Area. 2 Patients Had A

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Generalized Lymphadenopathy. Although Lymphadenopathy Involving Anatomic Sites Other Than Cervical Has Been Described In 2% To 40% Of The Cases, A Generalized Lymphadenopathy Is Infrequent .44% Patients Had Associated Fever, 8% Had Hepatosplenomegaly And 4 % Had Pancytopenia. More Than Two Thirds Of The Cases Had Lymphadenopathy Lasting For 2-3 Weeks Duration.

The Haematological Findings Associated With KFD Were Anaemia, Mild Elevation Of The Erythrocyte Sedimentation Rate, Mild Leucopoenia Or Leukocytosis With Atypical Lymphocytes In Peripheral Smear And Elevated C-Reactive Protein. Mild Leucopenia Has Been Seen In 20- 58% Of Patients, Probably Due To Cytokine-Mediated Mechanisms[5] And Up To 25% Of Patients May Show Atypical Lymphocytes In Their Peripheral Blood, Pointing To A Viral Aetiology. SLE Was Ruled Out In All Patients By Serology.

The Lymph Node Biopsy Is Mandatory For The Diagnosis Of KFD. No Radiographic Finding Specific To KFD Has Been Established To Make A Concrete Diagnosis. The Findings Of CT And Magnetic Resonance Imaging Of KFD Can Be Variable And Mimic Not Only Lymphoma But Also Various Nodal Diseases With Necrosis, Including Metastasis And Tuberculosis.[6] In Patients With Typical Clinical Features And Characteristic Cytological Findings In Lymph Node Aspirates, FNAC Alone Would Suffice For Diagnosing KFD.[7] The Points That Favour Diagnosis In Cytology Are Lymph Node With Necrosis, Karyorrhectic Debris, Crescentic Histiocytes And Conspicuous Absence Of Granulocytes. The Characteristic Histopathologic Findings Of KFD Include Distortion Of Nodal Architecture With Irregular Areas Of Fibrinoid Necrosis And Abundant Karyorrhectic Debris In The Paracortex With Plenty Of Histiocytes Of Various Types, Immunoblasts And Plasmacytoid Cells And A Notable Absence Of Granulocytes.[1,2,3,4,8]

In Our Study, Partial Or A Complete Effacement Of Lymph Node Architecture Was Seen In All Cases And Reactive Follicles With Well Developed Germinal Centres Were Present Only In 5 Cases. Widening Of Paracortex With A Starry Sky Appearance Was Seen In 40% Of The Cases. This Was Due To The Presence Of Transformed Lymphoid Cells (Immunoblasts) Surrounded By The Light Staining Proliferation Centres Which Showed A Mixture Of Transformed Lymphocytes, Immunoblasts, Plasmacytoid Cells And Histiocytes.[8] Apoptotic Or Karyorrhectic Debris Of Varying Degrees Was The Characteristic Finding In Almost All Cases. In Some, It Was So Widespread As To Almost Resemble Areas Of Geographic Necrosis. Neutrophils And Eosinophils Were Characteristically Absent, And Plasma Cells Were Scarce.

The Classification Of The Histopathologic Features Of KFD By Kuo Into Proliferative, Necrotizing, And Xanthomatous[9] Types, Was Applied In Our Study. According To Kuo, The Most Common Type Was The Necrotizing Type, Accounting For Slightly More Than Half Of The Cases. In Our Study Too, 56% Were Of Necrotic Type And 44% Were Of Proliferative Type. Foam Cells Were Not Seen In Significant Numbers As To Include Any Of Them To The Xanthomatous Group.

Though The Histomorphological Examination Of Involved Lymph Nodes Is The Mainstay For The Correct Diagnosis Of Kikuchi Disease, The Recognition By Morphology Frequently Presents A Challenge To Many Pathologists, Because Of Its Features Simulating Lymphoma Or Reactive Lymphadenopathy Due To Other Causes.[3, 4] Hodgkin Disease Can Show Plasma Cells And Histiocytes But The Presence Of Typical RS Cells And

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Plenty Of Eosinophils Help To Differentiate Hodgkin Lymphoma From Kikuchi Disease.[10] Non Hodgkin Lymphoma Which Can Resemble KFD Clinically And Microscopically, Due To Presence Of Necrosis And Large Cells, Are Anaplastic Large Cell Lymphoma (ALCL) And Diffuse Large B Cell Lymphoma (DLBCL). The Cells Accompanying Necrosis Are Histiocytes, Plasmacytoid Cells And Immunoblasts In Kikuchi Disease While Atypical Lymphoid Cells And Larger Cells Are Seen In Anaplastic Large Cell Lymphoma.[10]

The IHC Using 10 Markers Was Done To Look For The Expression In Three Cell Groups-The Histiocytes, Immunoblasts And Plasmacytoid Lymphocytes. The Expression Pattern Is Described In The Results.

Normally, Histiocytes Do Not Express MPO (Myeloperoxidase) In Their Cytoplasm And The Expression Of MPO In Histiocytes Is Peculiar To KFD And Lupus Lymphadenitis.[11] 50-80% Of Histiocytes In Our Study Showed A Strong Cytoplasmic MPO Positivity In 15/25 Cases. Rest Of The Cases Were MPO Negative Probably Because Of The Geographic Necrosis Involving Them. Pileri *Et Al*[2] Observed That 25% To 75% Of Lesional CD68+ Histiocytes Co Express MPO. So MPO Positivity Can Be Diagnostic In KFD, Although It Cannot Differentiate KFD From Lupus Lymphadenitis.[11] 44% Of The Histiocytes Cases Showed Membranous EMA Positivity Ranging From 30-60% (Mean 36.36) Of The Histiocytes (11/25 Cases). A Proportion Of Malignant Cells Of Anaplastic Lymphoma Kinase (ALK) Positive ALCL Are Positive For EMA.[10] But They Are Morphologically High Grade Cells. In KFD, EMA Positivity Is Seen In The Bland Looking Histiocytes. The Absence Of CD30 Expression By The Histiocytes And Plasmacytoid Dendritic Cells Helps To Rule Out ALCL In Which The Large Cells Will Be CD30 Positive. Lack Of Expression Of CD20 Within The Large-Cells Can Rule Out A DLBCL. A Proliferation Of Immunoblasts And Clusters Of Plasmacytoid Dendritic Cells In Kikuchi Disease Could Potentially Mimic A Large-Cell Lymphoma Like Peripheral T-Cell Lymphoma, Due To The Expansion Of Paracortex In Both Entities. But $CD8^+$ T Cells Predominate In KFD, Peripheral T-Cell Lymphomas Are Mainly $CD4^+$ Cell Type.[10, 12]

Systemic Lupus Erythematosus Is The Most Challenging Differential Diagnosis Of KFD Histologically.[13, 14] Both Show Variable Degrees Of Paracortical Necrosis With Karyorrhectic Debris And Inflammatory Cell Response, Including Histiocytes. But In Contrast To KFD, SLE Lymphadenitis Often Demonstrates Aggregates Of Degenerated Nuclear Debris (So-Called Hematoxylin Bodies) And Aggregates Of Degenerated Nuclear Material In The Walls Of Blood Vessels (Azzopardi Effect).There Will Also Be A Prominent Reactive Follicular Hyperplasia, Abundant Plasma Cells, And Capsular Or Pericapsular Inflammation, As Well As Sparse, Cytotoxic T Cells. In KFD, By Contrast There Will Be A Predominance Of $CD8^+$ T Cells, Absence Of Neutrophils, And A Relative Paucity Of Plasma Cells. Careful Evaluation Of The Patient's Clinical History And Laboratory Data, Including The Evaluation Of Antinuclear Antibodies Will Help. It Should Be Emphasized That In Patients With A Clinical Suspicion Of SLE Serology For ANA And Anti Dsdna Should Be Done To Prevent Delay In Treatment. Several Viral Infections Can Present With Paracortical Expansion With Necrosis And Histiocytic Infiltrate, Thus Mimicking KFD.[3, 10] But In General, Viral Lymphadenitis Has A Less-Prominent Histiocytic Infiltrates, More Neutrophils, More Plasma Cell Proliferations, And Predominant $CD4^+$ T Cells. Infection With Toxoplasma Gondii May Present

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With Histiocytic Infiltrate And Perifollicular Granuloma Formation; But Necrosis Is Uncommon. Necrotizing Granulomatous Lymphadenitis Of Tuberculosis, Histoplasmosis, Leprosy, And Cat-Scratch Disease Show Proliferations Of Epitheloid Cells, Giant Cells, And Granuloma. Necrotizing Lymphadenitis In Bacterial Infections Like Syphilis Is Associated With Perivascular Plasma Cell Infiltrates; And Eosinophils In Yersinia Infections. In All These Infectious Lymphadenitis Diseases, Etiologic Agents May Be Identified By Special Stains Or Immunohistochemical Stains.[3, 11, 12]

Conclusion

1. Diagnosis Of Kikuchi-Fujimoto Disease Largely Relies On The Histomorphological Features, Especially The Presence Of Necrosis And Apoptotic Debris With Plenty Of Histiocytes And Almost Complete Absence Of Neutrophils And Eosinophils.
2. IHC Markers Show Predominantly CD8 Positivity In Lymphocytes And Immunoblasts In Kikuchi Disease.
3. Cytoplasmic MPO Positivity In Histiocytes Is Helpful In Differentiating Kikuchi-Fujimoto Disease From Other Necrotizing Lymphadenitis And Lymphoma, Although It Cannot Differentiate It From Lupus Lymphadenitis.
4. EMA Positivity Is Seen In About 36.36% Of The Histiocytic Component Of Kikuchi-Fujimoto Disease.
5. CD30 Expression Of Larger Cells In Hodgkin Disease And Anaplastic Large Cell Lymphoma, A Close Differential Of Kikuchi Is Typically Absent Within Histiocytes In Kikuchi-Fujimoto Disease. However, Patients Diagnosed With Kikuchi Fugimoto Disease Are To Be Followed Up.

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Legends Tables and Figure

Table 1:

Marker	Histiocytes	Immunoblasts	Plasmacytoid monocytes
CD 3	0	20	0
CD 20	0	0	0
CD 8	0	19	0
CD 4	0	0	0
MPO	15	0	0
EMA	11	0	0
CD 30	0	6	0
CD 15	0	0	0
CD 56	0	0	0

*Frequency table showing positivity to IHC markers in the cellular component of Kikuchi disease

Table 2"

Marker	Histiocytes	Immunoblasts	Plasmacytoid monocytes
CD 3	0	70-80%	0
CD 20	0	0	0
CD 8	0	20-70%	0
CD 4	0	0	0
MPO	50-80%	0	0
EMA	30-60%	0	0
CD 30	0	30-40%	0
CD 15	0	0	0
CD 56	0	0	0

† Table showing range of percentage of cells expressing the antigen in marker positive cases

Figure.1. Age and sex distribution of cases

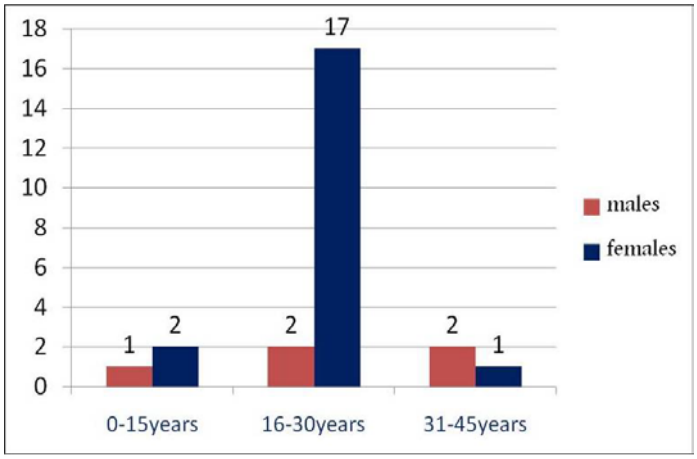
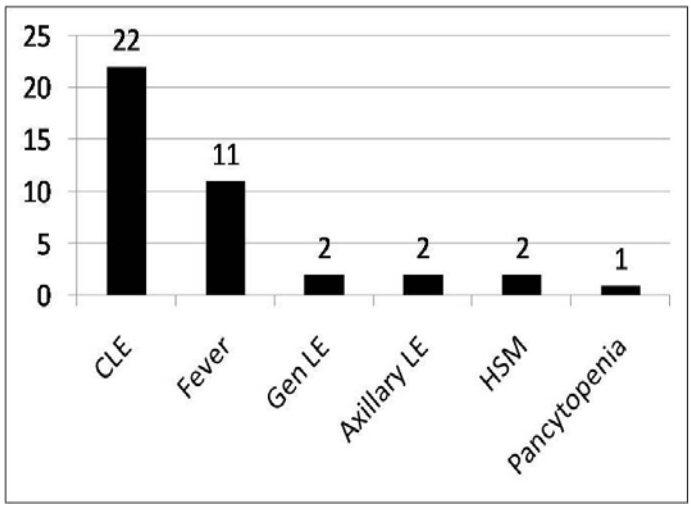


Figure.2. Bar chart showing clinical features



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