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RESEARCH ARTICLE

PRIMARY CUTANEOUS T-CELL LYMPHOMA (CTCL); CASE REPORT & REVIEW OF LITERATURE

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Abstract

Primary Cutaneous T-Cell Lymphoma (CTCL) poses a diagnostic challenge. The diagnosis can be delayed for years due to the similarities to common skin diseases such as psoriasis. The discrimination between clinical and histopathological is crucial for optimal diagnosis and treatment. The treatment of CTCL requires multidisciplinary approach and combinations therapy such as chemotherapy, biological therapy, & Extra-Corporal Phototherapy (ECP). Stem Cell Transplantation (SCT) plays a role in treatment of CTCL. Autologous Stem Cell Transplantation (ASCT) is associated with lower toxicities, but higher relapse rate, whereas Allogeneic Stem Cell Transplantation (Allo-SCT) is associated with lower relapse rate, but is associated with higher morbidity and mortality. Here we present a case of CTCL that was misdiagnosed as psoriasis and finally the correct diagnosis was reached and appropriate treatment was initiated. We here explore the diagnostic challenges and the therapeutic options.

Introduction:-

Primary cutaneous T-cell lymphomas (CTCL) are heterogeneous group of extra-nodal non-Hodgkin lymphoma, which is confined to the skin. The most common type of cell is T-cell derived which represents approximately 75% of the cases. It is classified into two main categories there are Mycosis Fungoid (MF), which has generally indolent behavior and Sezary Syndrome (SS), which is an aggressive and leukemic variant. MF and SS present with numerous variants that mimic benign skin conditions such as eczema, folliculitis, pigmented purpuric dermatoses, psoriasis, and vitiligo. Even after histological examination MF can resemble inflammatory dermatoses. MF can pose diagnostic challenges for dermatologist, but not for pathologist.[1]

Epidemiology:-

Surveillance, Epidemiology, and End Results (SEER) registry data, show the incidence of CTCL is the highest between male and African Americans. CTCL is not common in pediatric and young adult populations, often associated with histopathological variants of MF. The median age of diagnosis is mid-50s and increase 4-fold in patient over 70. Patient with MF and SS are significantly at increased risk of developing second lymphoma, Hodgkin lymphoma and CTCL subtype lymphomatiod papulosis as well as non-hematological malignancy.[1]

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Table I:- shows the new World Health Organization/European Origination for Research and Treatment of Cancer (WHO/EORTC) consensus classification for primary cutaneous lymphomas with relative frequency and 5-year Survival. [2]

WHO/EORTC Classification	Frequency (%)	5-year Survival (%)
Cutaneous T-cell and NK cell lymphoma		
A- Indolent		
Mycosis fungoiudes	**44%**	**88%**
• Follicular mycosis fungoides	**4%**	**80%**
• Pagetoidreticulosis	**< 1%**	**100%**
• Granulomatous slack skin	**< 1%**	**100%**
CD30+ lymphoproliferative disorders		
• Anaplastic large cell lymphoma	**8%**	**95%**
• Lymphomatoidpapulosis	**12%**	**100%**
• Subcutaneous panniculitis like T-cell lymphoma	**1%**	**82%**
• CD4+ small/medium pleomorphic T-cell lymphoma	**2%**	**72%**
B- Aggressive		
Sezary syndrome	**3%**	**24%**
Cutaneous peripheral T-cell lymphoma, unspecified	**2%**	**16%**
• Cutaneous aggressive CD8+ T-cell lymphoma	**< 1%**	**< 18%**
• Cutaneous γ/δ T-cell lymphoma	**< 1%**	**-**
Cutaneous NK/T-cell lymphoma, nasal type	**< 1%**	**-**

Etiology:-

MF is believed to develop as a result of chronic antigenic stimulation that leads to uncontrollable clonal expansion and the accumulation of T helper and memory T cells in the skin. Infections have been suggested have a role in development of MF particularly staphylococcus aureus (S. aureus). One study found high rates of S. aureus colonization's in patient with erthyrodermic MF (EMF) and SS with clinical improvement of both conditions after antimicrobial treatment of the infection. Most CTCL serologically are associated with human T-Lymphotropic virus type 1 (HTLV-1). Other viruses have been identified in patients with CTCL like Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) but the evidence that support virus as the etiology of disease is minimal. Immunosuppression medicationis considered an risk factors for development of the disease. Certain occupations can put the patient at risk to develop the disease such as working in the glass, pottery and ceramic industry, but still the evidence is controversial. Also, military exposure, herbicide exposure has been linked to non-Hodgkin lymphoma, but still non-specific to CTLC. [2]

Clinical presentation:-

1. Classic patients with mycosis fungoides (MF) present with slowly progressive disease over years. Patients can present with a patch plaque on the skin of non-exposed areas such as breast, buttocks, lower trunk and groin. These patch plaques progress to tumor at the end.
2. Sezery Syndrome (SS) and Erthyrodermic Mycosis Fungoides (EMF) are aggressive and leukemic CTCL variants characterized by atypical T- cell (sezery cell), diffuse (erthyroderma) and severely disabling pruritus with or without lymphadenopathy. Some may have non-specific dermatitis. SS usually arises de novo in short time or takes indolent course arising from Classic MF.
3. Erythrodermic MF presents with erythroderma and together with SS formerythrodermic CTCL. EMF is generally considered a progression of MF and distinguished from SS by absent or minimal blood involvement. A low burden tumor of circulating sezery cells is seen in the circulation without meeting the criteria of SS. The skin appearances in EMF range from mild erythema to generalized exfoliative with keratoderma and fissures on the palm and soles. These finding may be associated with hair loss, electrolytes imbalance, hypothermia and eyelid change/ ectropion. Also, these can be missed in elderly people and attributed to advanced age, drug reaction, or infection.Generalized Seborrheic Dermatitis, Psoriasis and Chronic Photosensitive reaction can resemble Erythrodermic CTCL. Table II blew shows the classification of international society of cutaneous lymphoma.[2]

Table II:-Proposed classification for erythrodermic cutaneous T-cell lymphoma and relative hematologic criteria developed by the international Society for Cutaneous Lymphoma in their consensus conference on erythrodermic cutaneous T-cell lymphoma. [2]

Erythrodermic CTCL	**Pre-Existing MF**	**Blood finding**	**Tumor, node metastasis, blood staging**
Sezary Syndrome (SS)	Rarely	Leukemic	T4, No-3, M0-1 B2
Erythrodermic MF	Always	Always	T4, No-3, M0-1 B-1
Erythrodermic CTCL not otherwise specified	Absent	Absent	T4, No-3, M0-1 B-1

CTCL, Cutaneous T-cell lymphoma; MF, mycosis fungoides.
B> 5% circulating Sezary cells;
B1, Sezary cell count of B> 1000 cell/m3 or >20% atypical T cell on peripheral smear, B2, Sezary cell count of < 1000 cells/m3 or <20% typical T cells on peripheral smear.

Case Report:-

32 years old male patient admitted with history of persistent skin lesion for eight years. The patient was diagnosed initially at the age of 24 as a case of psoriasis. He was managed as case of psoriasisfor period with clear slow progression of the disease until it reached the stage of Erythrodermic state with multiple nodules all over the body, with the largest under the right armpit reaching the size of basketball. The skin lesions were scaly erythematous plaque involving the whole body. Then, the patient was seen by a senior dermatologist at King Abdulaziz University (KAU) and skin biopsy was done which showed the diagnosis to be a CTCL rather than psoriasis. Because the patient was beyond the topical therapy for CTCL he was referred immediately to hematology department at KAU for consideration of systemic rather than topical therapy. The patient was very sick with fever and multiple skin discharges he was admitted to complete diagnostic evaluation and treatment plan discussion in the lymphoma tumor board. Peripheral blood film showed 3% of Sezary cells and pan CT scan of the whole body showed generalized lymphadenopathy without visceral involvement. Bone marrow aspiration and biopsy confirmed the presence of sezary cells in the bone marrow also confirming the state of sezary syndrome based on peripheral blood sezary cells rather than the bone marrow ones. Molecular cytogenetic studies did not reveal any abnormalities. The treatment options that were considered during the weekly hematology grand round are; systemic chemotherapy, local radiotherapy for large areas as a palliative intent, or surgical excision of the large tumor mass under the left armpit. The case was discussed in the lymphoma tumor board and in the city-wide lymphoma club and recommendation was made to commence chemotherapy of CHOP chemotherapy (Cyclophosphamide, Hydroxydaunorubicin, Vincristine (Oncovin), and Prednisolone) to be followed by allogeneic bone marrow transplantation (BMT) if feasible or autologous stem cell transplantation (ASCT) if possible. HDAC Inhibitors of Vorinostat can be considered after debulking with chemotherapy as maintenance therapy or after transplantation for minimal residual disease (MRD) eradication. The patient received eight cycles of CHOP with dramatic response and excellent mid treatment response upon evaluation clinically and radiologically. Three months later the disease came back again by reappearing of the skin lesions. Revaluation of the disease activity by clinical and radiological evaluation and re-biopsy to confirm the pathology was carried out. The patient was salvaged with **ESHAP** chemotherapy protocol (**E**toposide, **S**olumedrol (methylprednisolone), **H**igh dose cytarabine (**A**ra C) and **P**latinum (cisplatin)), for two cycles and he achieved very good partial remission and then he received two cycles of oral HDAC Inhibitor of Vorinostat. The plan was to perform ASCT after the biological therapy, at the same time we tried to arrange for Extra-Corporal Phototherapy (ECP) but both procedures were not feasible due to lack of ECP and lack of logistics to carry on ASCT. Patient expectedly progressed and developed new generalized plaque skin lesion and he was readmitted two months after the completion of the Vorinostat cycles. He was readmitted with multiple sites of infection and pus discharge and bacterial swabs showed strep.Alagctiae and S. aures. He was started on Co-Amoxiclav 625 mg tablet TID. Patient was evaluated again by the dermatology service and they recommended continuing fuisdic acid & Vaseline and no need for repeating the biopsy. Pan CT scan was done again and showed no visceral organ involvement and bone morrow aspiration and biopsy was done and did not show any involvement of the bone marrow. Patient was salvaged again with a third type of chemotherapy that is Gemcitabine based therapy of **GDP** (**G**emcitabine, **D**examethasone, &**P**latinum (Cisplatin)). He received the first cycle and in process to receive the second cycle to be followed by ASCT since he has a chemo sensitive disease and this time the biological therapy will be used after ASCT for MRD rather than before as it was done before.

Discussion:-

Table III:-illustrates the main differences between the two entities

CTCL	Plaque Psoriasis
Mid-50s.	Between 15-30.
Male and African Americans commonly affected.	White commonly affected.
Medication to treat HTN.	Medication to prevent malaria and lithium
No definitive risk factor except HTLV-1.	Common risk factor: stressful event, strep throat, cold or dry weather and cut, or scratch or bad sunburn.
1- Reddish patch plaque cover the whole of the body (no specific place). 2- Patch can be itchy. 3- Lymphadenopathy. 4- Patch prone to be ulceration. 5- Nail dystrophy. 6- Alopecia. 7- Edematous skin. 8- Hepatosplenomegaly.	1- Raised, reddish patch on the skin called plaque. 2- patches cover with sliver-white coat called scale 3- Most of the patch appears on the knee, elbows, lower back and scalp. 4- Patch can be itchy Scratching the itchy patch causing thickening of the patch. 5- Niall involvement.

This 32-year-old male who presented with large mass in right armpit and of the chest wall and scaly erythematous plaques that cover his whole body represented a therapeutic dilemma after confirming his original diagnosis. The option for treatment of this large mass was surgery, radiation therapy, or chemotherapy. After multidisciplinary and multiple presentations in tumor board and city wide lymphoma club a decision was taken to give this patient chemotherapy of CHOP. Patient received eight cycles with excellent response to treatment. Surgery for the large mass was not recommended by the surgeon because patient will need a large flab and his skin is already affect by the disease and the rate of complication after the surgery well be high, so surgery was not an option. Radiation therapy can be used only for palliation and intent in this patient was a curative treatment, so radiation will not be used here. The complications of radiation include alopecia, atrophy of sweet glands and of the skin, radiation induced dermatitis, skin edema, and skin squamous cell carcinoma is associated with high dose radiation. It is very important for the radiation dose to be given in fractions to prevent other complications. The total dose of radiation if exceeded 36 Gy the rate of the complication will be high also. The patient relapsed three months later after a complete response with chemotherapy. He was salvaged with ESHAP chemotherapy for two cycles with good response. Then, he was given HDAC inhibitor of Vorinostatfor two cycles for eradication of MRD and in preparation for ASCT. However, patient presented with his third relapse. He was readmitted to KAUH with multiple skin infections. His skin condition improved after starting antibiotics which suggested that skin infection may play role in development of this disease especially infection with S.aures. Patient was given a third line of chemotherapy of GDP to be followed by ASCT for disease eradication and this time Vorinostat will be used post ASCT as a maintenance therapy for MRD and prevention of relapse. At the same time we are still trying to arrange for ECP as a tool for disease control and eradication.

Risk-Stratification (Staging):-

In SS and MF TMNB (tumor, node, metastasis, and blood) play important role for the prognosis and help to form risk-adapted approach for the treatment. In 2007 TMNB have been reviewed by EORTC and ISCL for staging of MF and SS. If the patient has only one patch/plaque, then he has stage I, but stage I divided into two stages which are: stage AI (<10 % of the body surface is involved or T1) and stage IB (> 10% of the body surface is involved or T2) based on the extent of the skin disease. The Palm and the digits represent 1% of the body surface and this very helpful for clinical practice. The current recommendation of staging and diagnosis does not recommend biopsy of clinical normal lymph node, but it recommends when the size of the lymph node is more than 1.5cm. Dutch system, grade the lymph node staging system to be based on the presence of large cerebriform nuclei (7.5 um) and the degree of architecture effacement. In another staging system classification is based on the number of atypical lymphocyte (not the size) and the architecture of the node on the specimen to determine nodal involvement. In a patient with a patch/plaque stage T1/T2 and architecture perseveration of any abnormalclinical lymph node classified as limited-stage disease. The median age of these patients is measured in decades along with the survival of patient with stage AI. At the time of the diagnosis majority of the patients with MF have Limited-stage disease. On the other hand, patients with tumor stage (T3), erythroderma (T4), nodal involvement characterized by partial or

complete architecture effacement (N3), visceral metastasis (M1) or significant leukemic involvement (B2) have advance-stage disease. The median survivals 1-5 years are observed in patient with extensive disease.[1]

The modalities of the treatment of MF/SS:-

HDAC inhibitors (Histone deacetylase):-

HDAC Inhibitors are a new group of biological therapy that works on epigenetics. HDAC is catalyzing the removal of acetyl group from both Histone and non-Histone proteins. HDAC inhibitors affect Histone proteins which are responsible for gene expression in cell-cycle and apoptotic regulator protein while non-Histone proteins are involved with regulation of cell growth and survival, angiogenesis, aggresomal formations and DNA repair. Also, it affects the micro-environment of the tumor via reactive oxygen species. It enhances antigens presentation and down-regulation of immunodulatory cytokines, like IL-10. Vorinostat (suberoylanilind hydroxamic acid, SAHA) and romidepsin (depsipeptide) inhibit class I and II HADCs and both drugs are being used in lymphoprolifetive disorder due to high effectiveness of these novel therapy. The overall response rate is 30% in of advanced stage disease and the median duration of response to the drug is estimated to exceed 185 days but most responses were rapid <two month in patient with SS. Side effect of the these new medications include GI (nausea, vomiting, diarrhea) and hematological (anemia and thrombocytopenia). Vorinostate may cause prolong QT interval. The table shows the side-effects of the medication.[1]

Table IV:-Zolinza™ (vorinostat) clinical or laboratory adverse events occurring in CTCL patients (incidence ≥ 10% of patients). [3]

	Zolinza 400-mg once daily (n = 86)			
Adverse events	**All grades**		**Grades 3–5***	
	n	**%**	**n**	**%**
Fatigue	**45**	**52.3**	**3**	**3.5**
Diarrhea	**45**	**52.3**	**0**	**0.0**
Nausea	**35**	**40.7**	**3**	**3.5**
Dysgeusia	**24**	**27.9**	**0**	**0.0**
Thrombocytopenia	**22**	**25.6**	**5**	**5.8**
Anorexia	**21**	**24.4**	**2**	**2.3**
Weight decreased	**18**	**20.9**	**1**	**1.2**
Muscle spasms	**17**	**19.8**	**2**	**2.3**
Alopecia	**16**	**18.6**	**0**	**0.0**
Dry mouth	**14**	**16.3**	**0**	**0.0**
Blood creatinine increased	**14**	**16.3**	**0**	**0.0**
Chills	**14**	**16.3**	**1**	**1.2**
Vomiting	**13**	**15.1**	**1**	**1.2**
Constipation	**13**	**15.1**	**0**	**0.0**
Dizziness	**13**	**15.1**	**1**	**1.2**
Anemia	**12**	**14.0**	**2**	**2.3**
Decreased appetite	**12**	**14.0**	**1**	**1.2**
Peripheral edema	**11**	**12.8**	**0**	**0.0**
Headache	**10**	**11.6**	**0**	**0.0**
Pruritus	**10**	**11.6**	**1**	**1.2**
Cough	**9**	**10.5**	**0**	**0.0**
Upper respiratory infection	**9**	**10.5**	**0**	**0.0**
Pyrexia	**9**	**10.5**	**1**	**1.2**

Table IV summarizes the frequency of specific adverse events, regardless of causality, in CTCL patients using the National Cancer Institute-Common Terminology Criteria for Adverse Events, version 3.0 (Olsen et al 2001; Foss et al 2005).

Extracorporeal photophoresis (ECP):-

In extracorporeal photoresist, the product of leukapheresis and plasmapheresis are exposed to 8-mthoxypsosralen (8-MOP) before extracorporeal circulation through 1-mm thick disposable cassette exposed to UVA radiation. The

irradiations of leukocytes represent about 5% of the peripheral blood leukocytes in circulation and are given back to the patient. Psoralens covalently bind and crosslink DNA after UVA exposure and this leads to cellular death by several mechanisms. On the other hand, ECP leads to monocytes activation which stimulate antigens presenting cell and gene expression change leading to enhancement of the immune response. To use this finding there is a new protocol "trans immunization "where the blood products incubated overnight before following UVA radiation. This protocol not commonly used due to the risk of the infection and lack proven efficacy. Following the landmark study by Edson et al. describing response in 27 out 37 patients with erythrodermic CTLC treated by ECP, ECP was approved by Food and Drug administration (FDA) of USA for treatment CTCL and now is considered the first line of management of patients with SS in many centers. The response to the treatment varies between different case series, and the overall response rate is 60% and complete response rate is around 20%. In current protocols of treatment with ECP, oral administration 8- MOP is no longer required. ECP is generally well tolerated by the patients with schedule of of two consecutive days every two to four weeks. The mechanism of action of ECP is not completely understood. ECP has immunomodulatory effect which augments the immune response (host anti-tumor immunity). So, the median time to response is approximately six month. Median survival time after the treatment exceeds eight years as it has been observed in these patients. A lot of patients experience a durable response which may permit for some weaning from CTCL directed therapies. Some factors may affect the response to the treatmentespeciallyif there is significante nodal or visceral involvement. Also, ECP can be combined with other therapy such as interferon, or bexarotene. [1]

High-dose chemotherapy and hematopoietic stem cell transplantation:-

In CTCL the use of autologous stem cell transplantation is derived from case series study, but the durable response for treatment is observed after allogenic stem cell transplantation. This finding may be explained by the graft versus lymphoma immune response. A retrospective analysis of 60 patients with advanced-stage who underwent allogenic stem cell transplantation was recently reported. In this study, the patients had received a median of four prior therapies before the allogenic stem cell transplantation using a conditioning of either reduced-conditioning (73%) or myeloablative (27%) conditioning before related (75%) or matched-unrelated donor (25%) transplantation. Mortality rate for non-relapse at one year was only 14% for patients who received reduced intensity conditioning or HLA identical/related donor stem cell and 38 to 40% for those who received myeloablative conditioning or match-unrelated donor graft. Transplantation during early phase of treatment was associated with relapse rate (25 vs. 44%) and a statistically insignificant increase 3-years overall survival (68 vs.46%). The use of match-related donor was associated with superior overall survival (63% at 3 years). 17 out of 26 patients who relapsed received donor lymphocyte infusion. 47% achieved complete remission and this provides evidence for graft-verse-lymphoma effect in MF/SS. On the other hand, the experience with B-cell non-Hodgkin lymphoma, chemotherapy sensitivity before the transplantation or the extent of the burden of the disease did not influence overall survival. The conjunction of total skin electron beam therapy with allogenic stem cell transplantation may consider in selected cases. [1]

Conclusion:-

Cutaneous T-cell Lymphoma (CTCL) can be difficult to diagnose. In our case report the patient received four lines of systemic therapy that included three lines of chemotherapy (CHOP, ESHAP, & GDP) and one line of biological therapy (HDAC Inhibitor; Vorinostat) that halted the disease progression, but due to recurrent skin infections disease reactivation and progression occurred. A plan of high dose chemotherapy followed by stem cell rescue is planned to eradicate the disease and to be followed by biological therapy of Vorinostat for Minimal Residual Disease (MRD) eradication.

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