SnapshotDx Quiz: December 2021

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WHAT IS YOUR DIAGNOSIS?

Figure 1. Images courtesy of Fabrizio Galimberti, University of Miami (consent for publication of the images has been granted by the patient).

Editorial note: Welcome to the Journal of Investigative Dermatology (JID) Snapshot Dx Quiz. In this monthly online-only quiz, the first question ("What is your diagnosis?") relates to the clinical image shown, while additional questions concern the findings reported in the JID article by Quaglino et al. (2021) (https://doi.org/10.1016/j.jid.2020.07.026).

Detailed answers and a list of relevant references are available following the Quiz Questions below.

QUIZ QUESTIONS

1. What is your diagnosis based on the two clinical images?

A. Lepromatous leprosy

B. Neurofibromatosis

C. Mycosis fungoides

D. Amyloidosis

E. Leishmaniasis

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2. Which of the following answers is TRUE?

A. The neoplastic cells in mycosis fungoides (MF) are of cytotoxic phenotype cells with features of memory cells.

B. There is constant expression of CD26 in both the skin and the blood of patients with Sézary syndrome (SS).

C. TOX, FYB, CCR4, and CD52 are biomarkers associated with better prognosis in cutaneous T-cell lymphoma (CTCL).

D. Signal transducer and activator of transcription (STAT) 4 is upregulated in early-stage MF and downregulated in late-stage MF. The latter is characterized by overexpression of STAT3.

E. In patients with MF and SS, circulating and skin-infiltrating T cells express low levels of PD-1.

3. Which of the following answers is FALSE?

A. MF and SS are characterized by extensive intratumor heterogeneity with divergent evolution of cancer subclones.

B. To identify the most suitable targeted therapy, clinicians should consider repeated molecular analysis from lesions of different sites and at different time points in MF and SS.

C. Upregulation of the genome organizer protein SATB1 in MF is associated with disease progression.

D. Brentuximab and mogalizumab have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of CTCL.

E. Currently, Jak and STAT inhibitors show promise in the treatment of MF and SS given the frequency of mutations in the disease pathway confirmed by whole-genome sequencing.

See following pages for detailed answers.

DETAILED ANSWERS

1. What is your diagnosis based on the two clinical images?

CORRECT ANSWER: C. Mycosis fungoides

This image depicts mycosis fungoides (MF). MF is the most common type of cutaneous T-cell lymphoma (CTCL), accounting for 50% of all primary CTCL cases. MF typically takes on an indolent course over years to decades, presenting with thin scaly patches or patches with wrinkled (pseudotrophic) appearance in sun-protected areas of the body. Over time, the patches progress to plaques and eventually tumors or erythroderma. Lymph node and visceral involvement and large-cell transformation typically occur in advanced stages. This patient exhibits multiple firm, infiltrative, skin-colored, and hypopigmented plaques and nodules on the face that involve the eyebrows (madarosis) and result in leonine facies. *Leonine facies* refers to facial disfiguring with prominent convexities and furrowed creases caused by the dermal infiltration of the skin, in this case, with neoplastic T lymphocytes. The differential diagnosis of leonine facies is broad but is most closely associated with lepromatous leprosy. Other conditions that must be considered include Paget's disease of bone, MF, amyloidosis, leishmaniasis, mastocytosis, sarcoidosis, and scleromyxedema.

Leonine facies has been shown to develop in a very small population of patients with MF. (Swerdlow et al., 2016). The tumors in MF usually arise from plaques over years, or even decades, and they are prone to ulceration. Tumors arising de novo without preceding patch or plaque stage are referred to as tumors d'emblee. It is now considered that most cases with tumors arising de novo probably represent primary cutaneous $CD30^+$ pleomorphic, medium or large-cell T-cell lymphomas. A patient with MF presenting only with tumors then requires revision of the diagnosis (Willemze et al., 2005).

Discussion of incorrect answers:

A. **Lepromatous leprosy:** Although leonine facies can be found in lepromatous leprosy, usually the skin infiltration is not limited to the face. Lepromatous leprosy presents with multiple symmetrical erythematous violaceous lesions that can develop into hypopigmented macules, papules, and nodules. The infiltration typically spares warm areas of the body, leaving the most affected areas to be the face, scalp, ears, fingers, and toes (Reibel et al., 2015). If left untreated, lepromatous leprosy is usually accompanied by loss of touch, temperature, and pain sensation. Lepromatous leprosy is caused by *Mycobacterium leprae* and may be transmitted by respiratory droplets. The diagnosis of leprosy is made from the clinical picture but must be complimented by skin bacilloscopy and histopathology.

B. **Neurofibromatosis:** Neurofibromatosis is a multisystem genetic disorder with hallmark cutaneous findings, including café au lait macules, neurofibromas, pigmented hamartomas of the iris, and axillary freckling. Neurofibromas usually do not become apparent until puberty and may continue to increase in size and number throughout adulthood. Usually, the face will be involved with characteristic soft, pea-sized bumps on or under the skin, with involvement of other areas on the body (Gutmann et al., 2017).

C. **Amyloidosis:** Amyloidosis encompasses a group of diseases that are characterized by the extracellular deposition of amyloid. It can be divided into three entities: deposition of an abnormal protein (monoclonal light-chain immunoglobulins) as in acquired systemic amyloidosis, deposition of non-immunoglobulinemic acute phase proteins as in reactive systemic amyloidosis, and for unknown reasons as in wild-type transthyretin amyloidosis (Wechalekar et al., 2016). The deposition of eosinophilic extracellular material in body tissues typically shows apple green birefringence with Congo red staining. It may be localized or systemic and is almost always associated with plasma cell dyscrasia. Systemic findings can be related to involvement of the heart, muscles, gastrointestinal tract, kidneys, and nerves. Mucocutaneous lesions can be seen in 30–40% of patients and may present before systemic involvement is apparent (Flores-Bozo et al., 2019). Cutaneous findings include infiltrated eyelids resulting in bilateral, symmetrical, waxy, confluent papules with or without secondary purpura. Severe infiltration may cause visual impairment and cosmetic deformity. Less common skin signs include smooth waxy infiltration of the palms and volar fingertips, poikiloderma, sclerodermatous changes, alopecia, nail dystrophy, and bullous lesions (Bohne et al., 2004). Diffuse non-scarring alopecia has also been reported as a presentation of systemic amyloidosis in about 20 cases, including alopecia universalis (Miteva et al., 2015).

E. **Leishmaniasis:** Cutaneous leishmaniasis results from infection of the skin with obligate intracellular parasites of the *Leishmania* genus. The parasites are transmitted by the bite of infected female phlebotomine sandflies. Typically, the primary lesion starts as erythema at the site of a sandfly bite. The primary lesion may then evolve over weeks to months to a nodule, which may ulcerate with an elevated violaceous rim. Leishmaniasis exhibits sporotrichoid spread with pruritus and pain. Diffuse cutaneous leishmaniasis is a rare variant caused by

L. aethiopica that is seen more commonly in patients with HIV. It can cause disseminated, nonulcerated lesions that can mimic the lesions of lepromatous leprosy (Kumari et al., 2018).

2. Which of the following answers is TRUE?

CORRECT ANSWER: D. Signal transducer and activator of transcription (STAT) 4 is upregulated in early-stage MF and downregulated in late-stage MF. The latter is characterized by overexpression of STAT3.

The STAT signaling pathway plays a major role in multiple different functions of the cell, including apoptosis. Because Jak/STAT signaling regulates transcription of genes involved in cell division, dysfunctional proteins in the pathway can lead to several neoplastic processes. For example, STAT3 is linked to serious tumors, such as melanoma (Groner and von Manstein, 2017). For this reason, many STAT inhibitors have been developed to target most specifically STAT3. Additionally, the STAT pathway plays a central role in inflammation. Chronic inflammation is a hallmark of CTCL, which results in overexpression of STAT4. This overexpression has been described in the early stages of CTCL. STAT4 downregulation in CTCL is related to the switch of the phenotype from T helper type (Th) 1 to Th2. The overproduction of Th2 cytokines is due to recurrent point mutations and deletions in the ZEB1 zinc finger transcription repressor that has been found in 56–65% of CTCL cases. This phenotype switch to Th2 results in tumor growth in CTCL (Choi et al., 2015; McGirt et al., 2015; Wang et al., 2015).

Discussion of incorrect answers:

A. **The neoplastic cells in MF are of cytotoxic phenotype cells with features of memory cells:** The statement is false. CD4 memory Th cells are the types of cells in MF and Sézary syndrome (SS). In early stages of the disease, neoplastic cells are few and are of the reactive Th1 and CD8 phenotype, which is an antitumor phenotype. In the course of the disease and in the advanced stages, neoplastic cells acquire the ability to switch to the tumorigenic Th2 phenotype. Th2 cytokines IL-4, IL-10, and IL-13 are increased and, with their immunosuppressive properties, cause the progression of the disease and growth and spread of the tumor. In the leukemic form of SS, the malignant cells are central memory cells, whereas in MF, these cells have an effector or resident memory phenotype. In both MF and SS, the skin expresses L selectin and CCR7 (Krejsgaard et al., 2017).

B. **There is constant expression of CD26 in both the skin and the blood of patients with SS:** This statement is incorrect. There is a constant loss of CD26 in skin and peripheral blood in SS. The loss of T-cell markers has been reported in SS, and it is associated with poor prognosis, especially the loss of CD26. CD26 is an extracellular peptidase whose high expression has been traditionally used as an indicator of immune activation and effector functions in T cells. It is constitutively expressed on endothelial and epithelial cells of various tissues and on more than 50% of peripheral blood lymphocytes in healthy subjects, and its expression is enhanced by T-cell mitogens or antigens. CD26 is detectable on neoplastic cells of most anaplastic large-cell lymphomas and in a proportion of T-cell non-Hodgkin lymphomas (Bernengo et al., 2001). Low expression of CD26 can result in a lack of apoptosis in certain T cells (Salgado et al., 2012). The loss of expression of CD26 is a characteristic feature of Sézary cells. The lack of CD26 expression is a useful diagnostic parameter of peripheral blood involvement in patients with SS (Bernengo et al., 2001).

C. **TOX, FYB, CCR4, and CD52 are biomarkers associated with better prognosis in CTCL:** This is incorrect. CD52 (Campath-1 antigen) is a glycoprotein of 12 amino acids anchored to glycosylphosphatidylinositol. It is widely expressed on the cell surface of immune cells, such as mature lymphocytes, NK cells, eosinophils, neutrophils, monocytes/macrophages, and dendritic cells. Flow cytometry is more sensitive than immunohistochemistry in detecting CD52 expression. Flow cytometry can specifically detect expression on the cell surface of CD52, whereas immunohistochemistry cannot (Zhao et al., 2017). Gene expression profile studies have been used to identify molecular markers related to a higher risk of disease progression from early to advanced phases of MF. High expression of CD52 biomarkers indicates advanced disease with poor prognosis. Lefrançois et al. (2018) also identified TOX, FYB, and CCR4 as markers for disease progression and decreased survival in CTCL.

E. **In patients with MF and SS, circulating and skin-infiltrating T cells express low levels of PD-1:** The statement is incorrect. There are high levels of circulating and skin-infiltrating T cells expressing high levels of PD-1 in MF and SS (Çetinözman et al., 2012; Samimi et al., 2010). PD-1 is a checkpoint protein on T cells, and when it binds to its ligand PD-L on normal or cancer cells, it prevents the cells from attacking other cells in the body. In cancer, the PD-1/PD-L1 or PD-L2 pathway is activated and is responsible for the activation of T cells with cytotoxic secretions against antitumor responses. Many studies have focused on these checkpoints and their

role in inflammation and subsequent development of the tumor to advanced stages. Patients with MF and SS who develop tumors have these genes mutated (Ungewickell et al., 2015).

3. Which of the following answers is FALSE?

CORRECT ANSWER: C. Upregulation of the genome organizer protein SATB1 in MF is associated with disease progression.

SATB1 is a genome organizer protein that has been found to be downregulated by STAT5 through the induction of miR-155; decreased SATB1 enhances the expression of cytokines such as IL-5 and IL-9 linked with MF disease progression (Fredholm et al., 2018). Poly-ADP-ribose polymerase 1, which is implicated in the regulation of several DNA repair pathways by modulating chromatin structure and interacting with different DNA repair factors, showed higher expression in aggressive disease and was found to be overexpressed in patients with early-stage MF who developed progressive disease (Fredholm et al., 2018).

Discussion of incorrect answers:

A. **MF and SS are characterized by extensive intratumor heterogeneity with divergent evolution of cancer subclones:** This statement is true. MF usually develops from resident memory T cells that express cutaneous leukocyte associated antigen and CCR4. Extensive clonal diversity with multiple T-cell clones has been found in the skin biopsy samples of one lesion or different lesions and in the peripheral blood as well. This heterogeneity and subclonal evolution plays a role in disease progression, and the skin lesions are continuously replenished by circulating malignant T cells. This explains the multiple, widespread skin lesions that become refractory to treatment with skin-directed therapies. This extensive intratumor clonotypic heterogeneity was not only detected on the level of a single lesion but also was detected among different lesions (Iyer et al., 2020).

B. **To identify the most suitable targeted therapy, clinicians should consider repeated molecular analysis from lesions of different sites and at different time points in MF and SS:** Repeated molecular analyses in different disease sites at different time points will allow clinicians to characterize the disease evolution from a molecular point of view. This will then allow clinicians to be able to identify the adequate targeted treatment modality, emphasizing the importance of repeating biopsies on patients. New therapeutic approaches that can improve disease outcome are now based on a better understanding of the molecular alteration and immune pathogenesis that is occurring in MF and SS. It has been shown that cutaneous MF lesions repeatedly replenish circulating neoplastic T-cell clones, which alters the mutation patterns, increasing the molecular heterogeneity, similar to consecutive tumor seeding. In addition to brentuximab and mogalizumab, a series of other potential drugs are in the pipeline that target other immune-modulating pathways, such as the PD-1 axis. With more choices becoming available for treatment, to ensure the best outcome for patients, a clear understanding of the molecular phenotype will guide targeted therapy (Quaglino et al., 2021).

D. **Brentuximab and mogalizumab have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of CTCL:** This statement is true. Brentuximab is an antibody–drug conjugate medication used to treat relapsed or refractory T-cell non-Hodgkin lymphoma. It selectively targets tumor cells expressing the CD30 antigen. In 2017, FDA and EMA approved brentuximab as a treatment for patients with CTCL who have received prior systemic therapy (Prince et al., 2017). Mogamulizumab is a humanized monoclonal antibody targeting CCR4. FDA and EMA approved mogamulizumab in 2018 for treatment of relapsed or refractory MF and SS (Kim et al., 2018).

E. **Currently, Jak and STAT inhibitors show promise in the treatment of MF and SS given the frequency of mutations in the disease pathway confirmed by whole-genome sequencing:** This statement is true. The Jak/STAT pathway functions to transmit signals from cell membrane to the nucleus. Gain of function mutations in the Jak family have been described in multiple different malignancies, including lymphoproliferative disorders. The Jak/STAT signaling pathway is implicated in CTCL pathogenesis (Netchiporouk et al., 2014), with overexpression of STAT4 in early-stage MF (Litvinov et al., 2014). A meta-analysis in 2017 identified nine studies with a total of 220 CTCL mutational data points and found 55 putative driver genes implicated in CTCL. From a therapeutic standpoint, 43% of these implicated genes harbor potentially targetable point mutations. Among these, the most frequently mutated belong to the T-cell activation/NF-κB pathway and Jak/STAT pathway (Park et al., 2017). Jak/STAT inhibitors have shown efficacy for the treatment of lymphoproliferative disorders as well as many other dermatological diseases, such as atopic dermatitis, psoriasis, and vitiligo. Multiple clinical trials are underway to evaluate the use of Jak/STAT inhibitors

in a variety of autoimmune and inflammatory diseases both topically and orally. Preclinical data suggest that Jak/STAT inhibition might be a viable strategy to treat multiple other dermatoses despite the myriad of potential adverse effects (Damsky and Choi, 2016).

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