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Review Article

CONCEPT OF CUTANEOUS T CELL LYMPHOMA IN AYURVEDA PERSPECTIVE AND ITS MANAGEMENT BY *SODHANA, SAMANA* AND *RASAYANA*: A REVIEW ARTICLE

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ABSTRACT

Cutaneous T cell lymphoma (CTCL) are a rare group of diseases caused by uncontrolled proliferation of T cells which belongs to mature T cell lymphoma having indolent nature. Two thirds of the CTCL are comprised of Mycosis Fungoides (MF) and Sezary Syndrome (SS). They are characterized by macules and patches which on later progresses to tumors or nodules with adenopathy and other organ infiltration. If left untreated the risk of developing infection increases with visceral involvement of skin, GI tract, lungs and adrenals. Diagnosis is done by histopathological appearance, cytogenetic analysis, etiology and the functional biology of neoplastic cells. Imaging techniques (MRI and CT) are widely done to assess the staging of disease and other tissue involvement. Radiotherapy, chemotherapy and retinoids have been in use since long time, but possess many side effects. According to Ayurveda, CTCL can be caused by *Ahara* like *Virudha, Agantuja bhavas, Beeja-beejabhaga-beejabhagavayava dushti* and *Ojas/bala hani.* The clinical features can be related with *Kushta* and in later stage simulates *Dhatugata kushta* and *Granthi-arbuda*. The etiopathogenesis of CTCL can be considered as formation of *Ama, Agnimandhya, Srothovaigunya*, and *Balahani.* Management will be preventive, curative and palliative with *Sodhana, Samana* and *Rasayana* therapies.

INTRODUCTION

T cell lymphoma is a rare type of cancer affecting T lymphocytes. Uncontrolled proliferation of T cells leads to formation of lymphoma which can become cancerous. At the cellular level, the evolution of cancer entails a multistep process involving mutation and selection for cells with progressively increasing capacity for proliferation, survival, invasion and metastasis.[1] Mutation in genes accelerates cell division rates and inhibits processes such as cell cycle arrest or programmed cell death. This altered regulation of cell cycle can lead to uncontrolled proliferation through which abnormal cells accumulate and ultimately cancer arises.

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The human immune response is mediated by the lymphoid system.

It imparts two types of immunity viz., innate immunity and adaptive immunity. Among this innate immunity is covered by Natural Killer (NK) cells and adaptive immunity by the B and T type cells. The understanding regarding these cells from their formation to maturation is needed for the diagnosis and management of this disease spectrum.[2]

T cell lymphomas include many varieties. Common being Peripheral T cell Lymphoma (PTCL), Cutaneous T cell Lymphoma (CTCL), Angioimmunoblastic T cell lymphoma (AITL), Anaplastic large cell lymphoma (ALCL), Adult T cell leukemia etc. Malignancies of NK cells are also included in the classification as they are closely related to T cells. As per WHO classification, T cell lymphomas are divided into Precursor and Mature T cell neoplasms. Precursor T cell lymphoma involves the expression of the lymphoblastic marker terminal deoxynucleotidyl transferase (TdT).[3] Mature T cell lymphoma is a group of rare aggressive lymphomas

that develop from mature white blood cells and originates from lymphoid tissues outside of the bone marrow. This group is again subdivided into leukemic, nodal, extra nodal and cutaneous.[4]

T cell lymphomas can be either indolent or aggressive. Among these indolent lymphomas has a long disease course and are generally resistant to standard chemotherapy, whereas aggressive disease is characterized by acute presentation with B symptoms (fever, night sweats, weight loss) and rapid progression. Cutaneous T cell lymphoma (CTCL) is considered indolent, whereas the peripheral mature lymphomas (PTCL), which include the rest, are considered aggressive. PTCL-NOS (not other specified) is the most common among the PTCL, followed by anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T cell lymphoma (AITL). Two thirds of the CTCL are comprised of Mycosis Fungoides (MF) and Sezary Syndrome (SS).[5] Here CTCL is considered.

Clinical Features

CTCL, as the name indicates, is characterized by skin lesions. MF is a chronic, slowly evolving T cell lymphoma usually confined to the skin in the early stages. Three sequential phases of disease include: patch, plaque and tumor stages. The initial lesions are flat, erythematous, scaling patches over the trunk and upper limbs but only cause inconvenience because of their appearance and pruritus. But when the disease progresses lesions turns to plaques. In the terminal stage tumors or nodules associated with lymphadenopathy, hepatosplenomegaly and other organ infiltration are seen. The rate of progression varies from 2 or 3 years to 20 years. SS is more aggressive, symptomatic and has lower remission rates presented with a generalized exfoliative erythrodermatitis and circulating atypical lymphocytes. Some of the precursor lesions associated with or which evolves into MF are clonal dermatitis, cutaneous lymphoid dyscrasias, follicular mucinosis, lymphoid papulosis, pagetoid reticulosis and granulomatous slack skin.[6]

Differential Diagnosis

The common differentials for CTCL include erythroderma like atopic/contact dermatitis, drug eruptions, erythrodermic psoriasis, lichen planus, cutaneous B cell lymphoma, subcutaneous panniculitis T cell lymphoma.[6]

Prognosis

At initial stages life expectancy will be same as that of healthier adults. When the disease progresses to become more infiltrative and causing visceral involvement, prognosis is bad. MF is lifelong and having recurrence after stoppage of treatment. SS has a poor prognosis with a median survival rate of 3-4 years.[6]

Complications

As immune system is weak, the patients are at high risk of infection. Also, there is high rates of secondary cancers especially lymphomas. Hyper calcemic and lytic bone lesions are involved in acute T cell lymphoma. Visceral involvement of skin, GI tract, lungs and adrenals are seen. Large cell transformation, which means more aggressive transformation is seen in CTCL. Ulceration of the lesion can be seen in MF.[7]

Management

There is no cure for CTCL, so treatment emphasize on clearance of lesions to bring about disease remission. The aim is to improve quality of life, increase disease free period and promote survival.[8] The management starts with correct identification of subtypes which requires repeated skin biopsies followed by clinicopathological correlation.[2] Skin biopsy helps in histopathological analysis and phenotyping. The gold standard for diagnosis of CTCL is not merely histopathological appearance. Each case should be assessed differently and diagnosed by the amalgamation of several diagnostic indices. Genotype analysis is mandatory as it is needed for the diagnosis of SS. Cytogenetic analysis, etiology and the functional biology of neoplastic cells can all provide diagnostic clue.[9] If a specific subtype is suspected, then testing for EBV PCR, HTLV-1PCR and celiac disease should be done.[2]

Computed Tomography (CT) is used to know the staging of disease. MRI is used to assess the soft tissue involvement in extra nodal NK/T cell lymphoma and subcutaneous panniculitis T cell lymphoma. FDG PET/CT scan have high sensitivity in some T cell lymphomas which aids in staging and assessing treatment response.[2] The staging of CTCL is based on the tumor, lymph node, visceral, blood (TNMB) system developed by the European Organization for Research and Treatment of Cancer (EORTC) and the International Society for Cutaneous Lymphomas (ISCL).[8]

Cancer has challenged the community with the adverse effects and unbearable expenses of available treatments. It has been marked as the second largest non-communicable disease after IHD (Ischemic Heart Disease). Extensive research has produced novel healing methods and hundreds of medications for the management of cancer. The saga extends from surgical excision to current radiation and chemotherapy. Radiation therapy is effective in controlling a variety of malignant tumors and is a component in the management of about half of all patients with cancer. Cancer chemotherapy involves the use of cytotoxic drugs and hormones. The treatment options available for CTCL are palliative, not curative. CTCL is progressive, can cause significant symptoms which

affect quality of life. Therefore, palliative care is adopted.

Therapy can be divided into topical therapy and systemic therapy. Topical therapy is skin directed meant for early stage disease in which lesions are confined to skin only and systemic therapy for later stage disease (advanced nodal or visceral disease). Topical therapy includes UVA with psoralen (PUVA), UVB, external beam radiation, total skin radiation, topical chemotherapy and topical retinoids.[3] PUVA inhibits DNA and RNA synthesis, but it will affect both normal and neoplastic cells and thus the side effect profile being secondary malignancies of the skin.[10] Systemic therapy is achieved by Interferon-alpha, oral retinoids, targeted therapies, single or combination chemotherapy and stem cell transplant. Corticosteroids are also used as both targeted and systemic therapy.[3]

Retinoids, biologically active derivative of vitamin A, are commonly used in the treatment of CTCL. It can be used as both topical and systemic. Commonly used topical regimens are bexarotene (FDA approved) and tazarotene. Systemic retinoids include acitretin, isotretinoin and bexarotene. Retinoids seems to have antiproliferative and antiapoptotic properties. Also, it possesses immunoregulation and induces DNA fragmentation. Severe hyperlipidemia, central hypothyroidism and teratogenicity are side effects of retinoids.[6]

Ayurvedic Aspect

All medical systems are usually based on canonical texts and are evolved parallel to biomedicine.[11] They have their own diagnostic and treatment modalities. In Ayurvedic perspective T cell lymphoma can be considered as the gross effect of systemic and metabolic alterations of the three *Doshas* and seven *Dhatus*. Previously cancer was thought to be a consequence of unusual sequential genetic events regulating cell growth and death. Now it is obvious that abnormalities involving epigenetic regulation, diet, environmental factors and immune function has a significant role in causing cancer.[12] T cell lymphoma cannot be merely considered as a skin lesion rather it is a metabolic syndrome. In Ayurveda classics the cancer is dealt under *Granthi-Arbuda*. Considering the symptoms, in the initial stages T cell lymphoma can be related with *Kushta* (skin diseases), but later stages can be considered under the perspective of *Granthi-Arbuda.*

The above-mentioned abnormalities can be considered as the *Nidanas* (etiological factor) categorized as *Aharaja* (diet), *Agantuja* (environmental toxins), *Beeja-Beejabhaga- Beejabhagavayava dushti* (Genetic predisposition) and *Ojas/Bala hani* (altered immunity). *Ahara* indicates the current change in dietic pattern which includes more incompatible and junk foods which have a role in changing the metabolism. It is dealt under the concept of *Virudha* mentioned in Ayurvedic classics. *Virudha* includes all type of diet which dislodges the *Doshas* but do not expel it out of the body.[13] Persons consuming them are prone to many diseases. While explaining the consequences of *virudha* Acharya Charaka has mentioned some skin conditions like *Visarpa, Kilasa* and *Kushta* which may be related with certain stages of T cell lymphoma.[14] Also diet with *Katu-amla-kshara rasa*, foods causing vitiation of *Rakta* like *Kulatha, Masha, Nishpava, Tila taila, Pindalu, Moolaka, jalaja-anupa mamsa, Dadhi* etc may contribute to the development of skin conditions.[15] *Agantuja bhavas* can be related with exposure of chemicals, use of cosmetics etc which also leads to the condition. *Beeja-beejabhaga-beejabhagavayava dushti* will favour the occurrence of disease. As *Twak* (skin) is considered as a *Matruja bhava* (factor derived from mother)[16] any derangement of genotype in mother may be a reason favourable for manifestation. Also, during the stage of *Douhrida* if the mother ignores the longings, *Dosha prakopa* happens leading to *Vinasa* or *Vairoopya* of the child.[17] In *Sukradhatu gata kushta*, it is said that the doshas affect semen and ovum transferring it to the succeeding generation.[18] Immunity is related with *Ojas* and *Bala*. Among the three types of *Bala, Yuktikrita bala* depends on *Ahara, Vihara* and *Aushadha.* The factors hampering this particular *Bala* affects the immune status of body making it susceptible to disease. Also, *Ojas* otherwise explained as *Bala* is considered as the essence of seven *Dhatus*. Three types of abnormalities of *Ojas* are mentioned by Acharya Susruta such as *Visramsa, vyapat* and *Kshaya*. In *Ojovyapat*, *Varnabheda* is one of the symptoms which is a sort of skin manifestation.[19] Altered immunity favours the occurrence of the disease. Altogether above factors are interrelated which predisposes to development of lymphoma.

The *Samprapthi* (pathophysiology) of T cell lymphoma can be framed on the basis of concepts such as *Tridosha*, *Saptha dhatu* and *Agni*. As *Twak* is mainly involved here, the site where pathogenesis happens may be the *Twak* itself. While explaining the layers of *Twak,* the upper layers are the stratum of manifestation of skin conditions like *Sidhmam, Kilasa, Kushta, Visarpa* etc. The 6th one *Rohini* is the site of manifestation of *Granthi-arbuda*.[20] So here in later stages of T cell lymphoma deeper layers get affected. The exposure to *Nidanas* provokes the cardinal *Tridoshas*. The aggravation of *Pitta* and *Kapha dosha* produces an *Avarana* to *Vata* which in turn aggravates *Vata,* along with that it produces *Rakta dhatu dushti.*[21] Also, there is simultaneous *Saithilya* of *Dhatus.* The *Vata* along with other two *Doshas* reaches *Bahya rogamarga* lodges in already vitiated *Dhatus* such as *Twak, Rakta, Mamsa* and *Lasika* producing the

symptoms. If left untreated it invades the deeper *Dhatus* i.e., in the stage of formation of tumor or nodule with adenopathy. This can be best explained in terms of *Dhatugata kushta* mentioned in Ayurveda classics. In the extensive cellular level, this may evoke inflammatory changes which disturb *Agni*. Imbalanced *Agni* leads to disabled metabolism in the *Dhatus*. Also impaired *Agni* causes formation of *Ama* leading to *Srothorodham* (obstruction of channels). So, in T cell lymphoma, there happens a *Tridosha dushti* with *Pitta-kapha* predominance. The involved *Dhatus* are *Twak, Rakta, Mamsa* and *Lasika* initially. *Srothas* affected are *Rasavaha, Raktavaha, Mamsavaha* and *Swedavaha* with *Sanga* and *Vimargagamana* type of *Dushti. Rogamarga* is *Bahya* and *Adhishtana* is *Twak*.[22] The symptoms become more severe as it approaches deeper *Dhatus*.

Scope of Ayurveda

As already said, this cancer is resistant to chemotherapy. This is often because of the development of resistance against chemotherapy and intolerance of the patients to the established and toxic chemotherapy. There arises the scope of Ayurveda. There is no definitive cause for T cell lymphoma, but can be linked with various factors mentioned earlier such as *Aharaja* etc. Therefore, the aim of management will be reversing the pathology, conservation of *Agni,* maintaining the bodily tissues in their excellent forms and to improve quality of life.

With the omics revolution, emergence of translation and personalized medicines led to the development of drugs on the basis of subtype for cancer patients.[12] Ayurveda have given much importance to personalized drugs considering their status of *Doshas, Dhatus* and *Agni*. Personalized drugs aim at systemic correction rather following a fixed protocol. So, choosing medicines will be according to condition of patient.

Ayurvedic Management

The treatment of T cell lymphoma can be dealt under three main heads viz., Preventive, Curative and Palliative. In preventive aspect, one should rely mostly on healthy diet and regimens avoiding the use of incompatible junk foods, exposure to toxins etc. The aim here is to maintain the health of healthy individual- "*Swasthasya swaasthya rakshanam*." Those who have a positive family history can adopt this preventive method to avoid its occurrence in future. Also, this can be adopted for women prior to conception. *Rithu sodhana* (elimination of *Doshas* in corresponding seasons periodically)[23] is good to prevent the disease occurrence in those with genetic predisposition. *Rasayana prayoga* is good to attain a healthy disease-free state. *Kamya rasayana* has a significant role in attaining *Prana* (vitality and longevity), *Medha (*mental competence), *Sri* (bodily lustre and complexion). Those which contain *Amalaki* (gooseberry) can prevent such as they possess antioxidant property and act as free radical scavengers. Studies showed its strong skin protective ability as it enhances the fibroblast proliferation and exhibits a highly significant photo-protective effect against UVB-induced toxicity.[24]

In curative aspect, T cell lymphoma can be tackled with medications and treatment procedures. It starts with correcting the *Agni* through *Deepana-pachana*, removing the *Doshas* from the site of manifestation through *Snehapana* (internal oleation therapy) and it's *Sodhana* (elimination) through natural orifices and finally administration of *Rasayana* for the wellness of *Dhatus*. *Deepana-pachana* is accomplished by administration of *Choornas* on the basis of predominant *Doshas*. Then administration of *Sneha Dravya* in *Ghritha* form is done to make an excitation to *Doshas* which should be started while we observe the premonitory symptoms itself. *Ghritha* is good to improve the complexion, proper functioning of sense organs and it is directly indicated in skin conditions. If it enters into a nodular stage *Taila* can be a better option but chosen on the basis of *Doshas* involved. *Madhyama matra snehapana* will be adopted here as it is indicated for *Arushka, Sphota, Pidaka* and *Kushta* conditions.[25] After *Doshas* get excited, *Sodhana* can be done either as *Vamana* or *Virechana*. Repeated *Snehapana* will be needed in between *Sodhana* if the condition is chronic which can be called as *Snehai: apyayana*.[26] The remaining *Doshas* can be pacified by *Samana* with administration of *Ghrithas* like *Tiktaka, Mahatiktaka, Vajraka* etc., in prescribed dose, external application of medications etc. When the *Doshas* gets removed, the impaired *Dhatus* can be reverted to normal state by administration of *Rasayana.* In the stage of macule-papule-patch etc., administration of *Chitraka, Somaraji* or *Tuvaraka rasayana* can be done. But when it attains nodular form, *Silajathu or Bhallathaka rasayana* will be better.

In palliative aspect, we can maintain the condition of patient without many complications and the hazardous effects of therapies. Also, the metastasis may be arrested through this. It is done for those who are contraindicated for *Sodhana*, in elderly, in those with reduced *Agnibala* and *Dehabala*, in later stage and those who can't tolerate the treatment modalities. The efficacy of *Rasayana avaleha* as adjuvant to radiotherapy and chemotherapy in reducing the adverse effects has already been proven.[27] *Chyavanaprasa* is one such formulation which exhibits cytoprotective, anticarcinogenic and antimutagenic activities and stabilizes the side effects of chemotherapy and radiotherapy. In an RCT on 75 patients of head and neck cancer, *Chyavanaprasa* (10 gm, twice daily) along with radiotherapy reduced the

severity of mucosal reactions and improved the Hb levels.[28]

DISCUSSION

T cell lymphoma possesses a broad etiopathology. Initially it mimics skin conditions (*Kushta*), but later it attains the stage of tumor and nodes (*Granthi-arbuda*). To hamper the pathogenesis adequate intervention should be done in initial stages itself. Correct identification of disease in appropriate time is needed to prevent the progression. The current therapies available can cause many ill effects which make the patient intolerant. Thus, Ayurvedic interventions have a significant role in this scenario. After assessing the involved *Samprapthi ghatakas* and health status of patient, management should be started giving prime importance to the preventive, curative and palliative aspect with elimination of *Utklishta doshas* and administration of *Rasayana* to build up the damaged tissues. Focusing on healthy diet and regimens is also essential in maintaining the benefits of these interventions. Once the disease progressed to an end stage, only thing can be done is to increase the longevity.

CONCLUSION

CTCL (Cutaneous T cell lymphoma) is a rare group of cancer with many influencing factors. The available treatment options such as radiotherapy, chemotherapy, retinoids etc., possess only palliative benefits. There is no complete cure and also the above therapies are resistant nowadays. Ayurveda emphasize on personalized medicine keeping the cardinal structural and functional components in its normalcy. Proper intervention in accurate time will helps to improve the longevity to a great extent. Proper *Sodhana, Samana* and *Rasayana* play a vital role in the management of CTCL. Further researches including clinical trials are needed in this area to explore the principles of Ayurveda.

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