



LYMPHATIC FILARIASIS LEADING TO SQUAMOUS CELL CARCINOMA AND ITS CONTROL: A BRIEF STUDY

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ARTICLE INFO

Article History:

Received 12th February, 2020

Received in revised form 23rd

March, 2020

Accepted 7th April, 2020

Published online 28th May, 2020

Key words:

Lymphatic Filariasis, Lymphedema, Lymphangitis, Lymphadenitis, Squamous cell carcinoma

ABSTRACT

Lymphatic filariasis, is a tropical disease caused by *Wuchereria bancrofti* & *Brugia malayi*, *Brugia timori* transmitted by *Culex*, *Anopheles*, *Aedes*, *Mansonia* mosquito. It mainly affects and swells the lymph nodes and lymphatic vessels of lower limbs, spermatic cords, epididymis when the adult worm blocks the lymphatic channels. Long decades living of this zoonotic parasite lead to lymphedema, lymphangitis, lymphadenitis etc. in association with of malignant changes including melanoma, lymphoma, Kaposi's sarcoma and squamous cell carcinoma(SCC). Here, we are going to discuss the unusual association between SCC and lymphatic filariasis and measures to its control or cure.

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INTRODUCTION

Lymphatic filariasis, is one of the tropical diseases and ranked the second leading cause of disability in the world by World Health Organization (WHO), caused by a thread-like zoonotic parasites or nematodes *Wuchereria bancrofti*, *Brugia malayi*, *Brugia timori* transmitted by *Culex*, *Anopheles*, *Aedes*, *Mansonia* mosquitoes. It affects primarily the lymph nodes and lymphatic channels of lower limbs, spermatic cords, epididymis & presenting the swelling of the affected region when the adult worms block the lymphatic vessels. Chronic lymphedema or elephantiasis is found to be associated with malignant changes including Kaposi's sarcoma, melanoma, lymphoma & squamous cell carcinoma. Chronic history of elephantiasis more than two decades leads to the genuine development of SCC, a life-threatening entity and if early diagnosed, can be controlled or cured (Gaurav Sahu *et al*, 2020).

Filariasis can be caused by both of the matured and larval nematodes, leading to 'classical filariasis' and 'occult filariasis'. Many case studies show that patients suffering from classical or occult filariasis, initially neglect the symptoms of lymphatic filariasis thus leading to surgical option only. To check elephantiasis from spreading inside the body, drug of choice for the past 40 years has been Diethylcarbamazine (DEC), Albendazole (ALB), Ivermectin (IVM), which eliminate the microfilariae from the blood and kill the adult worms.

But, now-a-days these drugs are no more highly effective in killing the long-lived adult worms. Thus a nematode-specific drug target for filariasis named Calumenin, a Ca²⁺ binding protein, is targeted and leading to the discovery of Itraconazole (ITC), which has inhibitory potential to inhibit a lanosterol 14- α -demethylase activity, thus presenting anti-fungal and anti-filarial activity (Tae-Woo Choi *et al*, 2018).

On the other hand, malignancy, mainly SCC, arising in chronic lymphedema, is a rare entity, majority of which are related to the limbs and breasts. Most of the studies suggest carcinogenesis in lymphedema to be associated with immunologic factors. Chronic lymphedema causes extrusion of protein into interstitial space with the influx of inflammatory mediators. Chronic inflammation is hypothesized as one of the major contributing factors for the development of malignancy due to poor hygienic conditions with infection following the involvement of bacteria into the edematous tissue. The early recognition of tumor-specific antigen is hindered by a shortfall in afferent lymphatic drainage. The possibility of a malignant growth in the lymphedematous tissue should be carefully handled. A dermatological opinion is to be taken as and when necessary. Chronic filariasis leading to SCC, has the only option of surgery. Serum tumor markers for penile SCC such as SCC antigen are considered as link between these two rare conditions and could play a crucial role in the detection of such complex cases (Laniado ME *et al*, 2003; Kommu S *et al*, 2005).

Regular measures and controlling steps have to be taken by the tropical country populations to prevent mosquito eradication

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by personal protections, chemically controlling the adult and larval stages of mosquitos and obviously by biological measures to actively prevent spreading of mosquito borne diseases, such as lymphatic filariasis.

Aims and Objectives

The main objective of this study is to take a view on the available resources from various other published papers on squamous cell carcinoma (SCC) caused due to lymphatic filariasis and its control for prevention of the spreading of elephantiasis among the tropical country populations and to establish a social awareness for common people, a self hygiene, measuring steps and using drug of choice or need of surgery to treat lymphatic filariasis and associated squamous cell carcinoma(SCC).

Pathogenesis of Lymphatic Filariasis & Associated Squamous Cell Carcinoma

Lymphatic filariasis is generally transmitted to man through mosquito biting and the third human infecting stage has an incubation period of 8-12 months.

Initially, after the infection, the affected individual shows an 'Asymptomatic Phase', having high microfilaremia and T_H2 stimulated immune response. 'Inflammatory Phase' is due to antigen released by the adult worms in the blood, causing dilation of lymphatic channels, interference with lymph flow and resulting in various symptoms like Lymphangitis (inflamed lymph vessels are seen as red streak due to circadian periodicity of the nematode towards peripheral lymph vessel), Lymphadenitis (repeated inflammation of lymph nodes with fever and chill), Lymphedema (swelling around neck, ankle, foot, arms, breast etc), Lymphorrhagia (rupture of lymph vessel and release of chyle), and Filarial fever. 'Obstructive Phase' is seen in heavy infection due to the obstruction of lymph flow through the lymph channels by the microfilariae; thus leading to Elephantiasis.

Here in this study, we are discussing on Squamous cell carcinoma by chronic lymphatic filariasis. SCC can be primarily appeared as thick, rough, scaly patch that bleeds or open sores that does not heal completely. Lymphatic vessel SCC is promoted by lymph angiogenesis that supports the abnormal growth and survival of adult cells.

Control and Therapy

The main two steps are to be taken to prevent and control lymphatic filariasis from root-i) Eradication of Vector mosquito
ii) Detection of carriers and proper treatment after that.

Control

Personal protection is to be taken viz. covering uncovered body part with clothings after sunset, using bio-ointments to prevent mosquito biting, curtaining doors and windows and walls of rooms to be painted with anti-mosquito paint, not to store stagnant water filled pot or ditches or drains and proper hygiene.

To destruct adult mosquitoes, 10% DDT solution is to be sprayed in shrubby wide areas behind the house. Very poisonous petroleum, Panama larvicide, Pairs green are to be sprayed at the mosquito breeding ground to eradicate mosquito larva. Fishes like *Gambusia sp.*, *Tanichthys albonubes* are voracious eater of mosquito larva and pupa. These fishes are to be

cultivated in stagnant water and cultivation of these may have effective biological control.

Therapy

For past 40 years, Hetrazan is used with a single dose of 6mg/kg, given annually or semiannually to the patients to eliminate microfilariae from the blood and careful administrations of Ivermectin (IVM), Albendazole (ALB) to kill to adult worms. Paramelaminayl phenyl stebonate is used to destroy the immature worms in lymphatic channels. Newly discovered novel-drug Itraconazole (ITC) has inhibitory property against the reproductive rate and cuticular surface sheath formation of nematodes causing filariasis, thus acting as anti-filarial agent and anti-fungal agent. Edematous limbs are sometimes successfully treated by applying pressure gauge or bandages, which forces the lymph or chyle as well as peripheral worms to come out of the swollen area.

Surgery is the most potent method to get rid of squamous cell carcinoma of skin tissue due to filariasis and some drugs are to be introduced as a prophylaxis. SCC of lymph nodes or lymphatic vessels or lymphangiogenesis leading to high rate of mortality but temporarily be checked with some surgical or chemotherapy or drug mediated therapies.

DISCUSSION AND CONCLUSION

The risk of suffering from lymphatic filariasis will be much more high in tropical country areas if active and passive measuring controls are not taken timely against the main reasons behind. Some squamous cell carcinomas (SCC) have at-least of 5-year survival rate in 99% of patients but stand as fatal if reach lymph nodes or lymph vessels due to chronic infection. Drugs of choice administration and surgery are the way to survive against lymphatic filariasis as a passive way. Destruction of vector species and early diagnosis of disease can lead to lowering the risk of elephantiasis as well as squamous cell carcinoma (SCC). A social awareness initiative among rural people, has to be taken by the Government. Establishment of campaign with a good hygiene, ethical and controlled conditions, has to ensure the optimal consciousness and safety.

Data Availability Statement

The datasets collected for the study are available to the corresponding authors.

Author Contributions

DM wrote the first draft. SA completed the manuscript, DM organized, designed the study and SA provided critical revision thoroughly. All authors read and approved the submitted version.

Funding

No supporting fund is provided.

Conflict of Interest

The authors declare that this study was completed without any interference of commercial or financial relationships.

Acknowledgements

The authors show their gratefulness to their academic institution.

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How to cite this article:

Debalina Mukherjee and Subhechha Adhikary1 (2020) 'Lymphatic Filariasis Leading to Squamous Cell Carcinoma and its Control: A Brief Study', *International Journal of Current Advanced Research*, 09(05), pp. 22054-22056. DOI: <http://dx.doi.org/10.24327/ijcar.2020.22056.4346>
