Clinicopathological Study of Subcutaneous Heminthic Nodules: Unusual Sites and Diagnostic Dilemmas

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Superficial palpable swellings with heminthic infection as an underlying etiology is usually an accidental finding in the surgically excised specimens. Somatic nematodes and cestodes are the commonly implicated organisms, and the zoonotic nematodes show an emerging trend. The present study aims to reappraise the histopathological findings of heminthic etiology in superficial swellings which were clinically suspected to be of neoplastic/non neoplastic nature. Thirty six cases of palpable superficial nodules with infective etiology over a period of five years were reviewed. 19/36 were of heminthic etiology were included in the present study. Pertinent demographic and clinical data were retrieved from the medical archives. Amongst the 19 cases, 8 were males and 11 females. Chest wall (4/19), and eyelids (3/19) were the most common sites involved. The size ranged from 0.8-15 cm in greatest dimension. Presence of histiocytes (13/19), granulomas (11/19), eosinophils (10/19), and giant cells (9/19) were the most consistent histological findings. 14 cases had discernible parasite morphology with diagnosis of filarial worms (7/19), Dirofilaria (3/19), cysticercosis (4/19), and hydatid cyst (1/19). Four cases had dead and calcified parasites with no discernible morphology. Granulomatous inflammation and tissue eosinophilia are strong indicators of a parasitic etiology. Subcutaneous and intramuscular filariasis, cysticercosis and hydatid cyst are well documented etiologies whereas Dirofilariaisis is an emerging zoonotic infection with worldwide case reports. Imaging techniques and fine needle aspiration can point towards the diagnosis; however in the absence of characteristic features, histopathology can be relied upon to diagnose a heminthic etiology.

Keywords: Cysticercosis; Dirofilaria; Filaria; Granulomas; Zoonoses.
frequency. Somatic nematodes and cestodes are the commonly implicated amongst the helminthic agents, and the zoonotic nematodes show an emerging trend with increasing number of case reports in literature.

*Wuchereria bancrofti, Brugia malayi,* and cysticercosis is responsible for most of the cases in India. Recently there has been an increase in subcutaneous nodules caused by *Dirofilaria* seen in various countries which was considered to be a zoonotic infection earlier.

The present study aims to evaluate and highlight the aetiological agents and the tissue diagnostic features of superficial lesions of helminthic etiology.

**MATERIALS AND METHODS**

This was a single institution, retrospective, observational study undertaken in the department of pathology of a tertiary care center over a period of five years (2012-2017). Thirty-six cases of surgically excised palpable superficial nodules unsuspecting a parasitic etiology were reviewed. Out of the 36, 19 cases diagnosed as having helminthic etiology were included in the study. Electronic archives and test requisition forms were used to collect pertinent demographic and clinical data including the age, sex, clinical diagnosis, site and size of the lesions. Hematoxylin and eosin (H&E) stained slides of the cases were retrieved, and histopathological findings were reviewed.

**RESULTS**

Amongst the 19 cases included in the study, 8 were males, and 11 were females (Age - Range 1-64) with a mean age of 36.36 years. Chest wall (4/19, 21%), and eyelids (3/19, 15.7%) were the most common sites involved. Forehead, neck,
| Case | Age (years) | Sex | Site                  | Size (cm) | Clinical diagnosis | Histopathology diagnosis |
|------|-------------|-----|-----------------------|-----------|--------------------|--------------------------|
| 1    | 35          | F   | Forehead              | 2x1       | Sebaceous cyst     | Dirofilariasis           |
| 2    | 64          | F   | Forehead              | 2.5x2     | Sebaceous cyst     | Filariasis               |
| 3    | 42          | M   | Neck                  | 2.5x1.5   | Lymphadenitis       | Abcess with dead filarial worm |
| 4    | 5           | M   | Right leg             | 1.5x1     | Cellulitis          | Abcess filariasis with   |
| 5    | 40          | M   | Chest wall            | 4x1.5     | Myositis            | Filariasis               |
| 6    | 25          | M   | Inguinal region       | 2x1.5     | Lymphadenitis       | Lymphadenitis with dead filarial worm |
| 7    | 38          | F   | Eyelid                | 0.8x0.5   | ? Tumor             | Dirofilariasis           |
| 8    | 44          | F   | Abdominal wall        | 4x3.5     | Dermoid cyst        | Cysticersosis            |
| 9    | 23          | M   | Chest wall            | 1.5x0.6   | ? Neoplastic        | Cysticersosis            |
| 10   | 26          | M   | Chest wall            | 3.5x2.7   | ? Neoplasm          | Cysticersosis            |
| 11   | 52          | F   | Right thigh           | 11x7      | Soft tumour tissue  | Hydatidosis              |
| 12   | 64          | F   | Right thigh           | 15x9      | Soft sarcoma tissue | Cysticersosis            |
| 13   | 46          | F   | Left eye              | 1.5x1     | Epidermoid cyst    | Abcess with dead filarial worm |
| 14   | 52          | F   | Chest wall            | 1.5x1     | ? Neoplasm          | Filariasis               |
| 15   | 16          | F   | Neck                  | 1.5x1     | Lymphadenitis       | Granulomatous inflammation with dead filarial worm |
| 16   | 49          | F   | Axilla                | 3x3       | Lymphadenitis       | Granulomatous inflammation with filariasis |
| 17   | 1           | M   | Eyelid (lower)        | 1x1       | Epidermoid cyst    | Dirofilariasis           |
| 18   | 33          | M   | Back                  | 2x2       | Lipoma              | Filariasis               |
| 19   | 36          | F   | Breast                | 1.7x1     | ? Carcinoma         | Filariasis               |
and thigh had 2 cases each (2/19, 10.5%), while axilla, abdominal wall, leg, inguinal region, breast, and back had 1 case each (1/19, 5.2%). The size ranged from 0.8 to 15 cm in the greatest dimension.

The clinical suspicion was neoplastic in 7/19 cases. Lymphadenitis was second most common in 4/19 patients followed by an epidermoid cyst in 3/19 patients, one each of sebaceous cyst, dermoid cyst, forehead cyst, cellulitis, and myositis. In none of the cases, an infective etiology was considered as a diagnostic possibility. The demographic details with clinical diagnosis are summarised in Table 1.

### Table 2. Histopathological findings and the associated organism

| Histopathology         | Filariasis | Dirofilaria | Cysticercosis | Hydatidosis | Deadcalcified worms | Cases (%) |
|------------------------|------------|-------------|---------------|-------------|---------------------|-----------|
| Indentifiable parasites| 7          | 3           | 4             | 1           |                     | 15        |
| Histiocytic infiltrate | 6          | 2           | 2             | 3           |                     | 13        |
| Granuloma              | 4          | 3           | 1             | 3           |                     | 11        |
| Eosinophils            | 4          | 1           | 2             | 4           |                     | 11        |
| Giant cells            | 2          | 2           | 2             | 3           |                     | 9         |
| Chronic inflammation   | 4          | 1           | 2             | 1           | 2                   | 10        |
| Acute inflammation     | 2          | 2           | 1             | 2           |                     | 7         |
| Necrosis               | 2          | 1           | 1             | 3           |                     | 7         |

**Fig. 2.** (A) Cross section of a filarial parasite with surrounding necrosis, and chronic inflammatory infiltrate (H&E, 100x). (B) Cross section of dirofilaria with surrounding foreign body granulomatous reaction (H&E, 200x). (C) Cysticercus larval form in the muscle tissue, the head shows protoscoleces (H&E, 100x). (D) Hydatid sand with few fragments of the laminated wall and occasional scolies (H&E, 100x)
A characteristic parasite morphology was seen in 15 cases (78.9%), while four cases showed dead or calcified parasites on extensive examination of the tissue. Amongst the other histopathological features, presence of histiocytes (13/19, 68.4%), granulomas (11/19, 57.8%), eosinophilia (10/19, 52.6%) were the top three histopathological findings. These findings were also consistently seen in the cases without a discernable parasite in the sections (Figure 1). Complete findings and the associated agents are summarised in Table 2.

The most common etiological agent seen in the histopathology specimens was filarial worms (7/19, 36.8%) followed by cysticercosis (4/19, 21%), dirofilariasis (3/19, 15.7%) and echinococcus (1/19, 5%) (Figure 2). 4/19 cases (21.1%) did not have a discernable parasite morphology, but a calcified remnant which was suspicious of a parasitic etiology.

DISCUSSION

A variety of arthropods, protozoa, and helminths infect the skin and subcutaneous tissues and can be identified by pathologists in cytology and histology preparations. The specific organisms depend on patient’s exposure history. Arthropods are the most common parasite seen and include Sarcoptes scabei, Demodex species and Tunga penetrans. Helminths are less often seen, and include round worms (eg, Dirofilaria spp.), tapeworms (eg, Taenia solium, Spirometra spp.), and flukes (eg, Schistosoma spp.).

Filaria is usually caused by nematodes including Wuchereria bancrofti, Brugia spp. and manifests primarily as lymphedema of the extremities, genitalia, and breasts. The most common presentations of W. bancrofti infestation are elephantiasis, chronic lymphedema, epididymitis, funiculitis, and lymphadenitis. Subcutaneous swelling is an extremely uncommon presentation of bancroftian filariasis even in endemic areas. In contrast to W. bancrofti, Loa loa commonly presents as a subcutaneous nodule. The cycle starts when a female Chrysops takes microfilariae from the blood of an infected individual during a blood meal. Then the microfilariae mature toward infective larvae (L3), which become infective and can be transmitted to another human during the next blood meal. In humans, filarial worms will develop to adult stage and then can produce microfilariae, which can be transmitted to the next individual during another blood meal. The microfilariae have a diurnal periodicity, appearing in the peripheral blood in the day time, and reach their maximum at around midday (11:00 am to 1:00 pm)12 The diagnosis of filariasis is by a demonstration of microfilaria in stained or unstained blood films, circulating filarial antigen detection and demonstration of organism in histopathological sections13. Other histological features seen with filariasis are foreign body giant cells, forming tubercle-like nodules. While intact microfilariae are not generally seen, there may be fragments of the parasite in the granulomata. The eosinophilic debris, in the form of Splendore-Hoeppli material can been seen surrounding the parasite14. The inflammatory reaction develops in nodular fashion around fragmented and necrotic worms. Epithelioid cells and foreign body giant cells appear subsequently. In the present study seven cases with filariasis was seen. Tissue histiocytic infiltrate (6/7 cases), granulomas (4/7 cases), and eosinophilia (4/7 cases) were the most consistent findings. Amongst the four cases with calcified worms, tissue eosinophilia (4/4 cases), histiocytes, granulunomas and foreign body giant cells (3/7 cases each) were the most consistent features, pointing to the fact that in the presence of such features an effort should be made to locate an etiology by taking more tissue sections.

Human subcutaneous dirofilariasis is a rare helminthic infection caused by filarial worms of the genus Dirofilaria, which is the natural parasites of dogs, cats, foxes, and wild mammals. Dirofilaria species belongs to the filarial nematodes, causes zoonotic infections in man, occasionally. Subcutaneous dirofilariasis is caused mainly by Dirofilaria repens, which causes subcutaneous nodules in and around the eye15. Human dirofilariasis due to D. repens has increasingly been recognized in India with most cases presenting with ocular manifestations15. Dirofilaria usually presents as subcutaneous nodule, either tender or nontender; occasionally migratory; and may be associated with an abscess. It is commonly found on the eyelids, scrotum, breasts, arms, and legs16. Mode of transmission of dirofilaria is through bite of an infected mosquito of the Culex and Anopheles species. Histologic
examination for species identification can be made by analysis of the length and morphology of the parasite; patients do not typically exhibit eosinophilia. *Dirofilaria* is characterized by a relatively large size, thick cuticle, and prominent musculature with muscle cells extending far into body cavity. Different *Dirofilaria* species can be distinguished by their size, thickness of cuticle, and presence or absence of longitudinal ridges. The presence of thick laminated cuticles, large muscle cells, and wide lateral chords is diagnostic for this parasite. Histopathological sections usually show cross section of the parasite with surrounding granulomatous tissue reaction with an intense inflammatory cell infiltrate composed of neutrophils, lymphocytes, and plasma cells along with foreign body giant cells. Despite *Dirofilaria* being a filarial nematode, the present study describes the cases separate from those of filariasis as it is an emerging zoonotic parasitic infection and not very well documented in the literature. The present study describes three cases of subcutaneous *dirofilaria*is affecting the eyelids. The most consistent tissue reactions were granulomas (3/3 cases), histiocytic infiltration, giant cells, and acute inflammatory infiltrate (2/3 cases each). Scanty tissue eosinophils were seen in one case.

Human cysticercosis is a potentially deadly infestation and is the consequence of ingestion of eggs of *Taenia solium*. Cysticercosis is the most common parasitic infestation of the central nervous system, muscle and subcutaneous tissue. About 54% of the patients present with subcutaneous nodules. Clinical features of cysticercosis shows numerous small papules and nodules, cysts in subcutaneous tissue, skeletal muscles, or mucous membranes, urticaria from leaking cyst fluid. Histological examination usually shows preserved parasitic morphology with calcuspheres. The host tissue reaction ranges from epitheloid to histiocytic to lymphocytic proliferation with or without a capsule. The parasite appears in the well formed cyst as usually distorted and often mummified. But the hooklets were relatively preserved up to the late stage. The present study describes tissue cysticercosis in chest wall in 2 patients and 1 each of abdominal wall and right thigh lesion. The histological findings include inflammation with eosinophilia (2/4 cases), histiocytic granulomas with giant cells (2/4 cases), necrosis (1/4 cases) and discernible worms in the microscopic examination (3/4 cases).

*Hydatid cyst* disease is an endemic parasitic infestation caused by *Echinococcus granulosus* and it is an important public health problem in the Mediterranean countries, Middle East, Africa, South America, Asia and Australia. It most commonly affects the liver (60–70%) while lungs are the second most common site (5–27%). If parasite passes liver and lungs, it may locate in any organ. Primary subcutaneous hydatid disease means that there is not any primary focus of hydatidosis. The main symptom of subcutaneous hydatosis was mobile painless, slow growing mass and only 30% of the patients complained with pain. Kayaa C etal reported the incidence of subcutaneous hydatid disease as 1.5% among all cases of hydatid disease in endemic areas. Serology is a useful tool particularly for the differential diagnosis of hydatid liver cysts, however, it is usually negative (79%) for subcutaneous hydatid cysts. Microscopically, hydatid cyst has 3 layers. Innermost (germinal layer) is 10–25 microns, contains nuclei, gives rise to brood capsules attached by short stalk in infectious (fertile) cysts, often with daughter cysts. Also protoscolices (attached or separated) with double row of refractile, birefringent, acid fast hooklets 22–40 microns and 4 round suckers that comprise “hydatid sand”. Daughter cysts may merge and provide internal septation. The second layer is a laminated membrane beneath germinal layer, which is 1 mm thick, avascular, eosinophilic, refractile and chitinous; strongly positive for Periodic acid Schiff, and Gomori’s methanamine silver. Outer layer is dense fibrovascular tissue with chronic inflammatory cells, variable calcification develops after over a long period of time if the disease goes unnoticed. The present study described a case of subcutaneous hydatidosis involving the right calf muscles, the tissue reaction showed a pericytic histiocytic infiltrate along with chronic inflammation, the debris on processing showed laminated memebanes, germinal layer and occasional protoscolices.

Fine Needle aspiration cytology (FNAC) is a safe, reliable, rapid and cheap method of evaluating swellings. It is well tolerated by patients and usually done as an outpatient procedure.
In cases of suspected malignancy, FNAC is a good choice as it prevents spread and in cystic swellings can be therapeutic. FNAC is currently being used for diagnosis of parasitic infections. Utility of FNAC in parasitic infections such as cysticercosis, filariasis and hydatid cyst disease has been well documented, but is not without pitfalls. The cytological specimen is then evaluated and smears are made of the aspirate for further evaluation. Parasitic infections are usually confirmed when there are demonstrable organisms in the smear along with other features of infections. Lymphocytic infiltration, particularly eosinophilic, along with giant cells, fibrous tissue are usually made out in the stained smears. In cases where there are no discernible organisms or parts thereof, biopsy with histopathological examination may reveal the diagnosis. Histopathological analysis helps in understanding the interactions between the host and the parasite and aids in the diagnosis where cytopathology does not reveal a conclusive diagnosis. In some cases like hydatid cyst disease, it is better to perform an excision than risk spillage of the hydatid fluid which can cause reactions.

Parasitic infections are on an increase in the recent years. Many factors or combinations of factors contributing to disease emergence include ecological changes, such as those due to human activities or to anomalies in climate; travel and immigration, technology and industry; microbial adaptation and change and breakdown of public health measures. The emerging infectious diseases are also attributed to the population growth, ageing population, poverty and malnutrition, environmental pollution, deforestation, crowding, inadequate infrastructure, poor sanitation and water supply, global warming, development of antimicrobial/insecticide resistance etc. In addition to this the immunocompromised patients, including patients with AIDS, solid organ transplant recipients, and patients on immunosuppressive therapy for disorders, are at high risk for opportunistic parasites.

CONCLUSION

Histopathological features like granulomatous inflammation and tissue eosinophilia are strong indicators of a parasitic aetiology. Subcutaneous and intramuscular filariasis, cysticercosis and hydatid cyst are well documented in literature whereas Dirofilariasis is an emerging zoonotic infection in the Indian subcontinent. Imaging techniques and fine needle aspiration can point towards the diagnosis with precision; however in the absence of characteristic features, histopathology can be relied upon to diagnose a helminthic aetiology.

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Conflict of Interest

There has been no conflict of interest in the present study.

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REFERENCES

1. Francesca D. Beaman, Mark J. Kransdorf, Tricia R. Andrews, Mark D. Murphey, Lynn K. Arcara, James H. Keeling. Superficial Soft-Tissue Masses: Analysis, Diagnosis, and Differential Considerations. Radio Graphics; 27(2):509–523 (2007).
2. Nawas ZY, Tong Y, Kollipara R, Peranteau AJ, Woc-Colburn L, Yan AC, Lupi O, Tying SK. Emerging infectious diseases with cutaneous manifestations: Viral and bacterial infections. J Am Acad Dermatol.; 75(1): 1-16 (2016).
3. Pampiglione S, Rivasi F, Angeli G, Boldorini P, Incensati R.M., Pastormerlo M., M. Pavesi, Ramponi A. Dirofilariasi due to Dirofilaria repens in Italy, an emergent zoonosis: report of 60 new cases, Histopathology 38: 344–354 (2001).
4. Goyal P., Sehgal S., Ghosh S., Mittal D., Kumar A., Singh S. A Cytological Study of Palpable Superficial Nodules of Parasitic Origin: A Study of 41 Cases. Patholog Res Int.; 2014: 373472 (2014).
5. Ratnatuna N., Wijesundera M. Histopathological diagnosis of subcutaneous Dirofilaria Repens infection in humans. Southeast Asian J Trop Med Public Health; 30(2); 375-78 (1999).
6. Norgan AP, Pritt BS. Parasitic Infections of the Skin and Subcutaneous Tissues. Adv Anat Pathol.; 25(2): 106-123 (2018).
7. Azad K, Arora R, Gupta K, Sharma U. Lymphatic
filariasis: Aspiration of adult gravid female worm from a soft tissue swelling. *J Cytol*; 27: 156-7 (2010).

8. Rosenblatt JE. Laboratory Diagnosis of Infections Due to Blood and Tissue Parasites. *Clin Infect Dis*; 49(7): 1103-1108 (2009).

9. D’Souza R., Jakribettu RP., Sudharsana S., Aithala SP. Subcutaneous nodule: A case of Dirofilaria. *Int J Appl Basic Med Res.* 3(1): 64-65 (2013).

10. Lupi O, Downing C, Lee M, et al. Macrocotaneous manifestations of helminth infections: Nematodes. *J Am Acad Dermatol*; 73(6): 929-944 (2015).

11. Kollipara R, Peranteau AJ, Nawas ZY, et al. Emerging infectious diseases with cutaneous manifestations Fungal, helminthic, protozoan and ectoparasitic infections. *J Am Acad Dermatol*; 75(1): 19-30 (2016).

12. Akue J, Eyang-Assengone E., Dieki R. Loa loa infection detection using biomarkers: current perspectives. *Res Rep Trop Med*; 9: 43-48 (2018).

13. Shenoy RK. Clinical and pathological aspects of filarial lymphedema and its management. *Korean J Parasitol.* 46(3):119–125 (2008).

14. C. Kayaalp. Hydatid cyst of the liver. L.H. Blumgart, R.J. Belghiti, R.P. DeMatteo, W.C. Chapman, M.W. Büchler, L.E. Hann, M. D’Angleca (Eds.), Surgery of liver biliary tract and pancreas (4th ed), Saunders Elsevier, Philadelphia, 952-970 (2007).

15. M.L. Eberhard. Zoonotic filariasis. R.L. Guerrant, D.H. Walker, P.F. Weller (Eds.), Tropical infectious diseases: principles, pathogens, and practice (3rd ed), Elsevier, New York; 750-758 2011.

16. Permi HS, Veena S, Prasad HK, Kumar YS, Mohan R, Shetty KJ. Subcutaneous human Dirofilariasis due to *Dirofilaria repens*: Report of two cases. *J Glob Infect Dis*; 3: 199-201 (2011).

17. S. Pampiglione, F. Rivasi, G. Canestri-Trotti. Pitfalls and difficulties in histological diagnosis of human dirofilariasis due to *Dirofilaria* (Nochiella) repens *Diagn Microbiol Infect Dis*, 34:57-64 (1999).

18. Srinivasamurthy V, Rao M S, Thejaswini M U, Yoganand. Human subcutaneous dirofilariasis. *Ann Trop Med Public Health*; 5:349-51 (2012).

19. Chi HS., Chi JG. A histopathological study on human cysticercosis. *Korean J Parasitol.* 16(2): 123-133 (1978).

20. Sacchidanand S, Namitha P, Mallikarjuna M, Nataraj H V. Disseminated cutaneous cysticercosis and neurocysticercosis: A rare occurrence. *Indian Dermatol Online J*; 3: 135-7 (2012).

21. N. Bal, N.E. Kocer, R. Arpaci, A. Ezer, F. Kayaselcuk. Uncommon locations of hydatid cyst *Saudi Med J*; 29: 1004-1008 (2008).

22. Kayaalp C., Dirican A., Aydin C. Primary subcutaneous hydatid cysts: A review of 22 cases. *International Journal of Surgery*; 9(2); 117-121 (2011).

23. Pedrosa I., Saiz A., Arrazola J., Ferreiros J., Pedrosa C. Hydatid Disease: Radiologic and Pathologic Features Complications. *Radio Graphics*; 20:795–817 (2000).

24. Arora VK, Singh N, Chaturvedi S, Bhatia A. Fine needle aspiration diagnosis of a subcutaneous abscess from enterobius vermicularis infestation: A case report. *Acta Cytol*. 41(6):1845-1847 (1997).

25. Yadav YK, Gupta O, Aggarwal R. Cytological diagnosis of parasites presenting as superficial nodular swelling: Report of 35 cases. *J Parasit Dis*; 36(1): 106-111 (2012).

26. So’tysiak Z, Rokicki J, Kantyka M. Histopathological diagnosis in parasitic diseases. *Ann Parasitol.* 60(2): 127-131 (2014).

27. Prasad K.J. Emerging and re-emerging parasitic diseases. *JIMSA*; 23(1): 45-50 (2010).