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Determinants and outcome of periocular dirofilariasis in a cohort of patients with demonstrable live worm from the ocular and adnexal parasitic granulomas

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Abstract

Purpose: *We attempt to describe the unique diagnostic features of dirofilariasis affecting the eye, a rare disease caused by the nematode dirofilaria repens.*

Case report: *The cohort includes 5 adult cases of ocular dirofilariasis. Migratory oedema was present in all but one case. The occurrence of the lesions near the medial canthus in all the cases including subconjunctival mass suggests predictable pattern of migration of the worm. Absence of systemic eosinophila and lack of marked eosinophilic infiltration around the parasitic granuloma in histopathology indicates alternative immune response against the parasite. Persistence of live worm despite antihelminthic drugs can be accounted by the presence of a thick capsule which protects the filaria against adulticidal and larvicidal drugs. Surgical exicision was curative in all cases.*

Conclusion: *Our case series points to the importance of having high index of suspicion and early detection of ocular dirofilariasis as it is amenable to simple and effective treatment.*

Key words: *Dirofilaria repens, zoonosis, migratory oedema, eosinophilia,*

Introduction

Dirofilariasis is an emerging zoonosis in India.[1] Pulmonary, cardiovascular, periocular, intraocular and orbital involvement has been documented both in endemic and nonendemic areas with dirofilariasis.[1,2] Scientific information available in the international literature is limited to isolated case reports from different parts of the world.[3] This data is insufficient to provide a clear and comprehensive concept regarding the clinical picture, investigative modalities and outcome of treatment in a case of suspected ocular dirofilariasis. Five cases of diagnosed ocular dirofilariasis are reported with an attempt to analyse the diagnostic features and treatment outcome of this rare but evolving entity.

Case details

This is a retrospective data analysis of cases diagnosed as periorbital and ocular dirofilariasis confirmed by demonstration of worm (either dead or alive) on excision biopsy during the period of one year. Informed consent was obtained from the

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subjects undergoing the treatment. Cases presumed as dirofilarial infestation where the worm could not be isolated were excluded. The cohort included five cases. The details are summarized in Table 1.

Table 1: details of cases of dirofilariasis

Table 1	Case1	Case2	Case3	Case4	Case5
Age	41	18	30	40	51
gender	F	F	F	F	F
Symptoms					
Duration	1 month	2 months	1 month	3 weeks	3 weeks
pain	+	+	-	+	+
itching	+	+	+	+	-
swelling	+	+	+	+	+
h/o Migratory itching with swelling	+	+	+	-	+
Signs					
redness	-	-	-	-	+
site	Subcuta-neous preseptal	Subcuta-neous preseptal	Subcuta-neous preseptal	subcuta-neous preseptal	subconjunctival
Size of the lesion	2cm x1cm	1.5cm x 1.5cm	1.5 cm x1cm	4 cmx2,5cm	0.5 x 0.5 cm
relation	Above medial canthus	Above medial canthus	Above medial canthus	below medial canthus	near caruncle
Consistency	Firm chord like	Firm chord like	cystic	Cystic nodule surrounded by urticarial skin oedema, mild tenderness	nodular
Eye	RE	RE	LE	LE	LE

Table 1	Case1	Case2	Case3	Case4	Case5
Eye examination	WNL BCVA 20/20 F=WNL	WNL BCVA 20/20 F=WNL	WNL BCVA 20/20 F=WNL	WNL BCVA 20/20 F=WNL	Subconj nodular tender swelling near caruncle,WNL BCVA 20/20 F=WNL
Investigations					
Blood routine	WNL	WNL	WNL	WNL	WNL
Peripheral smear	WNL	WNL	WNL	WNL	WNL
AEC	380	414	670	458	529
Pretreatment	Tab Albendazole , tab prednisolone X 3 weeks	Tab Albendazole , tab prednisolone X 3 weeks	Tab Albendazole , tab prednisolone X 3 weeks	Tab Albendazole , tab prednisolone X 1 week	---------
Excision					
capsule	Thick illdefined	Thick illdefined	Thick illdefined	Thick illdefined	Thick illdefined
Muscle infiltration	Orbicularis oculi	Orbicularis oculi	Orbicularis oculi	Orbicularis oculi	Medial rectus
pus	-	-	-	-	+
Status of worm	live	live	live	live	live
size of the worm	51 x 0.6mm	47 x 0.6mm	60 x 0.5mm	87 x 0.7mm	42 x 0.6 mm

Table 1	Case1	Case2	Case3	Case4	Case5
			HPR		
Tissue infiltration	Multi-lobulated fibrofatty infiltration	Multi-lobulated fibrofatty infiltration	Multi-lobulated fibrofatty infiltration	Multi-lobulated fibrofatty infiltration	Multilobulated infiltration
Eosinophils	scanty	scanty	scanty	scanty	Scanty
Epitheloid cells	++	++	++	+	-
Mast cells	+	+	+	-	-
Myositis	+	+	+	+	-
Fibrin	+	+	+	+	-
Recovery after excision	1 week	1 week	2 weeks	10 days	1 week

There is an increased incidence of newly detected or successfully treated cases of dirofiolariasis from Southern and Eastern Europe, Asia, and Sri Lanka.[2] India is being recognized as an endemic area for dirofilarial repens and immitis.[3] The cases are frequently reported from southern coastal states of Kerala and Karnataka.[4] But reports from Northern as well as Western India regarding dirofilarial infestation of the eye and periocular tissues are slowly emerging.[5,6] A total of 27 documented case reports on "human dirofilariasis" in India could be retrieved in the literature search on pubmed as on 30th june 2014. Most of them are periocular with a few cases of subcutaneous, intraocular and orbital involvement.[7,8] Our series of periocular and subconjunctival dirofilariasis is the largest cluster of such cases from a single institution over a period of one year.

All the cases in the study group were females. A review of literature showed that so far about 780 cases of human dirofilariasis have been reported worldwide.[8] Most of them are isolated case reports from both endemic and nonendemic areas. Hence no gender predilection has been noticed so far. This is the first report suggestive of preferential involvement of females. However, the bias may be due to a limited number of patients in this series. Mean age of the group was 36 years (SD 14.4); range 18 to 41. Dirofilariasis has been reported in subjects with age ranging from eleven months to 75 years.[9,10] The mean duration of symptoms was 32.4 days (12.96). In most case reports in the literature, the disease was shown to have a smouldering course with relapses which often contributed to diagnostic dilemma in such cases.[12] Left eye was involved in 60% cases.

Southern Kerala has been known as endemic for various species of filarial parasites, including dirofilarial infestation.[12] But no cases of dirofilariasis have been reported so far from northern Kerala. None of the cohort gave history of travel to endemic areas in and out of Kerala. Hence our series suggests the possibility of

endemicity in northern Kerala as well.

The symptoms at presentation were varied. Pain was present in 4/5 cases. Erythema was noticed only in one patient. Itching and swelling occurred in all patients. History of migratory oedema was appreciated by 4 subjects. Migratory oedema with itching is suggestive of subcutaneous larva migrans.

Migratory skin edema is frequently reported in dirofilarial infestation involving subcutaneous tissue in other areas of the body also.[13,14] The classical description is of creeping erruptions characterized by local swellings with changing locations. However continuous migration as in our series as well as isolated and scattered urticarial reactions have been reported. Similar findings have been noted among canine and feline community infested with Dirofilaria repens and immitis.[22] In them, pruritic dermatitis spreading to the adjacent region creating large areas of alopecia has been described.

Presence of itching out of proportion to the pain (and tenderness), associated urticarial reaction in the surrounding dermis, migration of the itchy oedematous areas contiguously to the adjacent site over a period of days and absence of leukocytosis and raised ESR led to the suspicion of dirofilarial infestation in the cases.

Dirofilariasis can present as an inflammatory mass or noninflammatory nodules.[14, 15] Among inflammatory cases cellulitis like presentation is rarely reported. Itching with or without tender swelling is the usual history. In our series all the cases with pain at the onset had live worms contrary to the observation that inflammation is often associated with dead worm due to arthus like response to the parasitic debris.[14] A careful history can give valuable clues regarding the diagnosis in such cases.

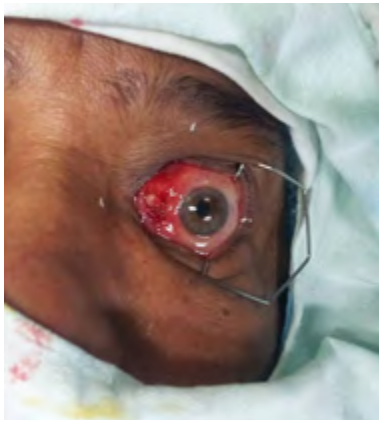

Fig. 1. Subconjunctival granuloma with live worm

Ocular involvement in dirofilariasis is usually periorbital, anterior orbital, subconjunctival, or subtenon.[16,17,18,19,20] This is because the worm has affinity for the subcutaneous tissues. In these cases, the worm is usually well localized. Rarely live worm has been isolated from anterior chamber. [21] Except for one case, all of our cases were subcutaneous. The swellings were above or below the medial canthus. The subconjunctival nodule was also related to the caruncle (Fig 1). Literature search revealed that most reported cases of subcutaneous periocular dirofilariasis are confined to the medial canthus. [16 -20] Many had history suggestive of larva migrans from the lower cheek and infraorbital areas.

The dirofilaria are accidentally transmitted to humans by bite of mosquitoes carrying infective larvae.[22] Dirofilaria cannot mature fully in human tissue and dies before producing microfilaria. The preferential involvement of the medial part of the eye, periorbita or caruncle in our series

suggests a predictable route of migration of the nematode towards the area. In animal eyes, it is postulated that several parasitic helminthes may be having trophism for eye and adnexa when migrating throughout host body during immature or adult stage.[23] The route which is followed to reach the eye is not clear.[23] Whether the worm reaches the face from a distant focus of mosquito bite or from a site of mosquito bite on the face cannot be commented. The worm takes one to two years to mature and start migrating.[23] The rate at which it wanders is not well understood. Is the eye preferentially involved or is it that, the facial involvement is easily noticed warranting early and definitive therapy is not evident. In the natural course of events, after wandering for months, the worm dies inciting an inflammatory response without any subsequent progression or sequele.[22] Reports of dirofilarial granuloma in areas like breast, scrotum, arms and legs which are considered as warm areas with rich vascularity, may be indicative of the fact that the increased vascularity of the periocular tissues may be the attracting force for these worms.[24] Or perhaps the immune mediated containment of the filarial parasite is better in areas with rich vascularity.

Eosinophils have been considered as the chief factors for local immunity against parasites.[6] Our observation contrary to this leads to a query whether there are other methods of immune responses in these cases. Complete blood picture and erythrocyte sedimentation rate were within normal limits with no evidence of eosinophilia. Peripheral blood smear was unremarkable, and no microfilariae were seen. Chest x-ray was also normal. No systemic eosinophilia was noted in all the five cases. The average absolute eosinophil count was 486.2 (SD 194.48). Eosinophilia is reported to occur in less than 15% of cases with D. immitis and rarely with D. repens.[22,23] The trichinella model suggests that sustained eosinophilic response to nematode infection may not reflect the effort of the host to clear the parasite. [25] They suggest that eosinophils can contribute to larval maturation. It is found that eosinophil deficiencies in experimental rats' compromised parasitic survival in chronic nematode infections.[26, 27] This theory may be applicable to dirofilarial infestations as well. Dirofilaria may alter the local immunity, preserving the nematode in the host. It may be the effort of the worm to maintain its position in the host. Eosinophilia which occurs during larval migration and maturation is hardly appreciable once the worm reaches the adult stage as in our series.

Four of the cases were initially and unsuccessfully treated with the oral antihelminthic drug albendazole. The drug was withheld in one case as excision biopsy was planned immediately on presentation. Surgical removal was eventually curative in all cases. Persistence of live worm despite antihelminthic drugs can be accounted by the presence of a thick capsule which protects the filaria against adulticidal and larvicidal drugs. In addition the ability of the filarial parasite to resist the inflammatory cell induced oxidative stresses in the host by the virtue of releasing antioxidant enzymes may be contributory.[27]

Surgical removal was curative in all cases. The patients showed fast recovery following removal of the worm. The average time of recovery was 9 days (SD 3.6). As the lesions were in the superficial plane, subcutaneous or subconjunctival, the

approach to the mass in each case was simple. However attachment to the underlying muscle, orbicularis oculi and medial rectus noted among all subjects in our series, has to be kept in mind.

Simple extraction of the worm is the treatment of choice for human dirofilariasis.[28] Unlike D. immitis which requires the use of anti-helminthic agents, use of antifilarial medication for D. repens is not indicated in the literature. In a small number of cases of D. repens, ivermectin and/or diethylcarbamazine has been tried with good results.

The plane of excision was difficult to ascertain due to the absence of a well defined capsule in all the cases. The worms, which were alive in all the subjects, were removed in toto. The surrounding tissue sample was taken for confirmation of the granuloma without disturbing the normal anatomy as far as possible in view of the close relation of the granuloma to the underlying muscle. The cystic cavity containing the worm showed pus only in case 5. However there were no significant signs of inflammation noted postoperatively.

There is no diagnostic blood test for ocular dirofilariasis. Sections of the worm showed thick cuticle with external longitudinal cuticular ridges and a thick muscle layer. Based on the morphologic features, the worm was identified as Dirofilaria repens in all cases (fig 2). Determining the species is more difficult, especially if a male worm is not present, and final diagnosis is often based on the presumed location of acquisition, antigen assay by PCR and integrated DNA barcoding of cox1 and 12S markers.[28] However, there are only a few centers globally where these investigative facilities are available. Imaging modalities like ultrasound with doppler, CT scan and MRI scan are described to be helpful in diagnosis of the cases.[29,30] They are useful in detecting cases in less accessible lesions like orbital masses mimicking malignancies. In our series the superficial location of the well localized cystic and firm nodules made them amenable to surgical excision, and high index of suspicion in this cohort was helpful.

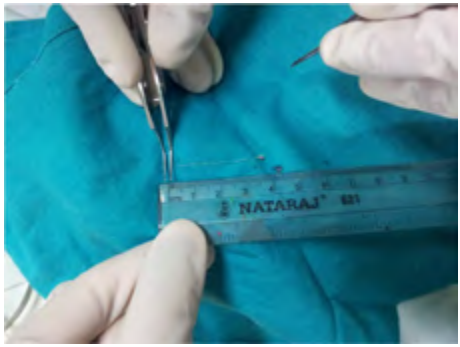

Fig. 2. 40 mm long live dirofilaria worm.

Histopathology revealed granulomatous changes with fibrin, inflammatory cells near the muscle and scanty eosinophils in four out of five cases (with longer duration of illness). (Fig 3,4) In the case where early biopsy was done there was no granuloma, fibrinous reaction and cells around the muscle. Recent studies have suggested that mast cells have an important role in parasitic inflammatory containment. [31] In the orbit, mast cells are found to be concentrated in the medial periorbita, which might account for the preferential localization of the dirofilarial granuloma in these areas. [31] The host tries to control the infection by granulomatous reaction around the worm. Mast cells also induce significant myositis resulting in

pain.[31] It is difficult to demonstrate mast cells in specimens as they are easily destroyed outside the body.[32] Frozen section may be an alternative to conventional specimen preparation to substantiate this hypotheses.

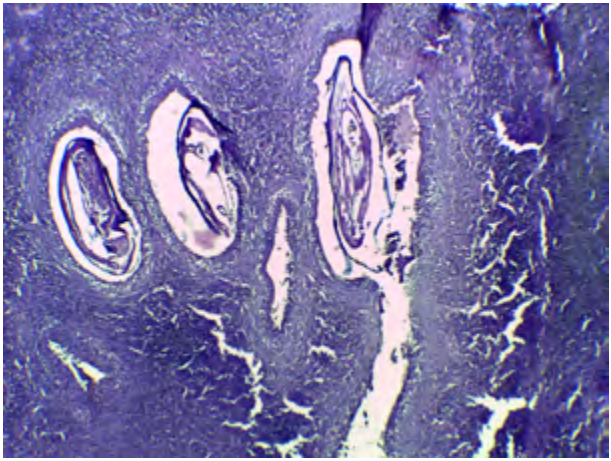

Fig. 3. Cross section of dirofilarial worm in tissue with surrounding granulomatous response H&E X40 300 dpi

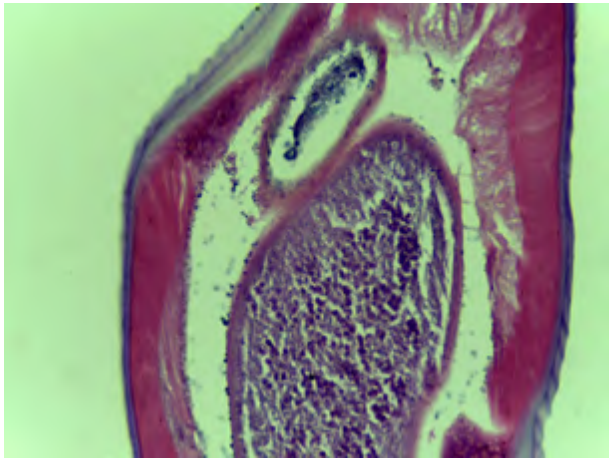

Fig. 4. Higher power view of cross section of worm H&E X200 300dpi

Conclusion

Ocular and orbital dirofilariasis continues to be recognized with increasing frequency, in new geographical areas and as a result of different species of parasites. Northern Kerala, a part of southern India may be an endemic area for this disease. We attempt to present a case series of five women with either ocular adnexal or subconjunctival infection of the nematode Dirofilaria repens. Each case presented with migratory edema, and most with pain and itching. Cases were resolved surgically, since worms persisted even with albendazole treatment combined with prednisolone. Eosinophilia was absent both systemically and locally. Tissues showed granulomatous pathology with myositis and fibrin deposition. Lack of reliable serological

assays, long life of the parasite in the host, varied patterns of presentation, often presumed diagnosis unless the worm is identified from accessible sites, selected involvement of subjects exposed to the same environmental risk and paucity of standard identification protocols for the worm, make management of dirofilarial infestations in and around the eye an enigma. Despite a small cohort with limited statistical power, the observations from our series provide directions in the evaluation and management of this rare but evolving entity. A high index of suspicion is mandatory in the prompt diagnosis, and surgical excision of such cases.

References

1. Boris Ilyasov, Vladimir Kartashev, Nikolay Bastrikov, Rodrigo Morchón, Javier González-Miguel, Fernando Simón; Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 19, No. 2, February 2013
2. Cutler SJ, Fooks AR, van der Poel WH: Public health threat of new, reemerging, and neglected zoonoses in the industrialized world. Emerg Infect Dis 2010, 16(1):1-7.
3. SL Hoti; Filariasis of uncommon nature in India; Trop Parasitol. 2012 Jan-Jun; 2(1): 2–3. doi: 10.4103/2229-5070.97230 PMCID: PMC3593514
4. Pauly M(1), Biswas J, Hussain RN, Anantharaman G; Periocular dirofilariasis mimicking lacrimal sac mucocoele. Orbit. 2013 Oct;32(5):324-6. doi: 10.3109/01676830.2013.814684. Epub 2013 Jul 29
5. Reema Nath, Sorbeswar Bhuyan, Himadri Dutta, Lahari Saikia Human subcutaneous dirofilariasis in Assam; Trop Parasitol.2013 Jan-Jun; 3(1): 75–78.
6. Sahdev SI, Sureka SP, Sathe PA, Agashe R; Ocular dirofilariasis: still in the dark in western India?; J Postgrad Med. 2012; 58(3):227-8.
7. Otranto D, Brianti E, Gaglio G, Dantas-Torres F, Azzaro S, Giannetto S ; Human ocular infection with Dirofilaria repens (Railliet and Henry, 1911) in an area endemic for canine dirofilariasis; Am J Trop Med Hyg. 2011 Jun;84(6):1002-4
8. Otranto D, Eberhard M L ; Zoonotic helminths affecting the human eye. Parasit Vectors. 2011 Mar 23;4:41.
9. Senanayake MP, Infaq ML, Adikaram SG, Udagama PV; Ocular and subcutaneous dirofilariasis in a Sri Lankan infant: an environmental hazard caused by dogs and mosquitoes. Paediatr Int Child Health. 2013 May; 33(2):111-2. doi: 10.1179/2046905512Y.0000000024.
10. Subbannayya Kotigadde, Sathyavathi Alva Ramesh, Kariyappa Thadiangada Medappa; Human dirofilariasis due to Dirofilaria repens in southern India;Trop Parasitol. 2012 Jan-Jun; 2(1): 67–68. doi: 10.4103/2229-5070.97247 PMCID: PMC3593497
11. Nath R, Gogoi R, Bordoloi N, Gogoi T. Ocular Dirofilariasis. Indian J Pathol Microbiol . 2010;53:157-9
12. Maryada Venkatarami Reddy; Human dirofilariasis: An emerging zoonosis;Trop Parasitol. 2013 Jan-Jun; 3(1): 2–3. PMCID: PMC3745666
13. Ajit Shriram Damle, Jyoti Anil Iravane (Bajaj), MuktaNagorao Khaparkhuntikar, Ganesh TarachandMaher, Rajashri Vilasrao Patil; Microfilaria in Human Subcutaneous Dirofilariasis: A Case Report. Journal of Clinical and Diagnostic Research. 2014 Mar, Vol-8(3): 113-114
14. Stringfellow GJ, Francis IC, Coroneo MT, Walker J ; Orbital dirofilariasis ; Clin Experiment Ophthalmol. 2002; 30(5):378-80.
15. Hoti SL, Tandon V. Ocular parasitoses and their immunology; Ocul Immunol Inflamm. 2011 Dec; 19(6):385-96. doi: 10.3109/09273948.2011.626141.
16. Strianese D, Martini A, Molfino G, Falabella L, Tranfa F ; Orbital dirofilariasis ; Eur J Ophthalmol. 1998; 8(4):258-62.
17. Joseph K, Vinayakumar AR, Criton S, Vishnu MS, Pariyaram SE; Periorbital mass with cellulitis caused by dirofilaria; Indian J Med Microbiol. 2011; 29(4):431-3.
18. Somsri Wiwanitkit, Viroj Wiwanitkit; Periorbital dirofilariasis; Indian J Ophthalmol. 2014 January; 62(1): 94. doi: 10.4103/0301-4738.126191 PMCID: PMC3955078
19. Basavaprabhu Achappa, Deepak Madi, Soundarya Mahalingam; An Interesting Case of a Subcutaneous Nodule;J Clin Diagn Res. 2013 February; 7(2): 364–365 ; doi: 10.7860/JCDR/2013/4737.2770 PMCID: PMC3592314

20. Ilyasov B, Kartashev V, Bastrikov N, Madjugina L, González-Miguel J, Morchón R, Simón F; Thirty cases of human subcutaneous dirofilariasis reported in Rostov-on-Don(Southwestern Russian Federation). Enferm Infecc Microbiol Clin; 2014 Jun 16. pii: S0213-005X(14)00181-5. doi:10.1016/j.eimc.2014.04.002.
21. Viney Gupta, Preeti Sankaran, Mohanraj, Jyotish Chandra Samantaray, Vimla Menon; Bilateral intraocular dirofilariasis ; Indian J Ophthalmol;2014 March; 62(3): 357–358. doi: 10.4103/0301-4738.116252 PMCID: PMC4061683
22. Walter Tarello ; Review Article Clinical Aspects of Dermatitis Associated with Dirofilaria repens in Pets: A Review of 100 Canine and 31 Feline Cases (1990–2010) and a Report of a New Clinic Case Imported from Italy to Dubai Journal of Parasitology Research Volume 2011, Article ID 578385, 7 pages doi:10.1155/2011/578385
23. Simón F, Siles-Lucas M, Morchón R, González-Miguel J, Mellado I, Carretón E, *et al;* Human and animal dirofilariasis; The emergence of a zoonotic mosaic; Clin Microbiol Rev. 2012;25:471–506. http:// dx.doi.org/10.1128/CMR.00012-12
24. J M Conly, L H Sekla, D E Low; Dirofilariasis presenting as a breast lump;Can Med Assoc J. 1984 June 15; 130(12): 1575–1576. PMCID: PMC1483366
25. Gottstein B, Pozio E, Nöckler K; Epidemiology, diagnosis, treatment, and control of trichinellosis; Clin Microbiol Rev 2009. 22(1):127-145.
26. Bruschi F, Murrell KD;Trichinellosis. In Tropical Infectious Diseases Principals, Pathogens, and Practices. 2 edition. Edited by: Guerrant RL, WalkerDH, Weller PF. Philadelphia: Churchill Livingstone. 2005:1225-1230
27. Kociecki J, Kociecka W; Visual system involvement in selected zoonotic diseases. II Trichinellosis; Klin Oczna 2004. 106(3):371-375.
28. Otranto D, Diniz DG, Dantas-Torres F, Casiraghi M, de Almeida INF, de Almeida LNF, Nascimento dos Santos J, Penha Furtado A, de Almeida Sobrinho AF, Bain O; Human intraocular filariasis caused by Dirofilaria sp., Brazil; Emerg Infect Dis. 2011.
29. M Smitha, VR Rajendran, E Devarajan, PM Anitha; Case report: Orbital dirofilariasis,Indian J Radiol Imaging. 2008 February; 18(1): 60–62. doi: 10.4103/0971-3026.37050PMCID: PMC2766890
30. Thandre N Gopinath, K P Lakshmi, P C Shaji, P C Rajalakshmi; Periorbital dirofilariasis—Clinical and imaging findings: Live worm on ultrasound; Indian J Ophthalmol. 2013 June; 61(6): 298–300. doi: 10.4103/0301-4738.114111 PMCID: PMC3744785
31. McMenamin PG, Morrison SM, McMenamin C; Immunomorphologic studies of mast cell heterogeneity, location, and distribution in the rat conjunctiva ; J allergy clin immunol. 1996;97(6):1375-86.
32. Ribatti D, Crivellato E; Mast cell ontogeny: an historical overview. Immunol Lett 2014 May-Jun; 159(1-2):11-4. doi: 10.1016/j.imlet.2014.02.003. Epub 2014 Feb 14.