
Spectrum of Pulmonary Hydatidosis in a Tertiary Care Center in Mumbai

Shivprasad Kasat, Unnati D. Desai and Jyotsna M. Joshi*

Department of Pulmonary Medicine, TNMC and BYL Nair Hospital, Mumbai Central, Mumbai- 400008 (Maharashtra) India

***Correspondence Info:**

Dr. J. M. Joshi,
Professor and Head,
Department of Pulmonary Medicine,
T. N. Medical College and B. Y. L. Nair Hospital,
Mumbai - 400008; India.
E-mail: drjoshijm@gmail.com

Abstract

Background: Hydatid disease, a parasitic infection caused by *Echinococcus granulosus*, has variable organ involvement. Pulmonary hydatid disease consists of a vast spectrum; a differential diagnosis to multiple lung diseases. We studied the clinico-radiological and therapeutic aspects of pulmonary hydatid disease.

Material and methods: This retrospective observational study was an analysis of patient records from 1997 to 2007. Twenty-three patients were included. Data was analyzed statistically in the form of frequencies and percentages.

Results: Mean age was 28.5 years. Men outnumbered women. Fourteen patients (60.86%) were from rural regions. Fifteen (65.21%) had contact with dogs. Cough was the predominant symptom (91.3%). Left lung was more involved than the right. The right lower lobe was the most common lobe involved. The commonest chest-radiograph finding was homogeneous round-to-oval opacity (52.94%). Commonest CT-thorax presentation was iso-to-hypodense opacity with enhancing wall. Eight (34.78%) had simultaneous liver involvement. Cyst size ranged from 2.8cms to 12.5cms. Indirect haemagglutination test was positive in 9(60%). Fourteen underwent surgery. Excision of the cysts with capitonnage was the preferred technique. Others were treated with albendazole in the dose of 10-15mg/kg/d for 3-6 months. Patients were followed at least up to 3 years without any mortality.

Conclusion: Pulmonary hydatidosis is not uncommon even in a non-endemic area with challenging diagnostics and management.

Keywords: Hydatid lung disease, *Echinococcus granulosus*, Albendazole, Doughnut sign.

1. Introduction

Hydatid disease is a parasitic infection caused by the larval stage of the tapeworm *Echinococcus granulosus*. [1] Hydatid disease can occur almost anywhere in the body and demonstrates a variety of clinical and imaging features that vary according to the growth stage, affected tissue and associated complications. Lung is second most common organ involved in hydatid disease next to liver. [1]

Pulmonary hydatid disease presents a wide range of clinical and radiological manifestations. Some are characteristic of the disease while others present a challenging diagnostic problem. It is a differential diagnosis to a spectrum of pulmonary conditions. In past few decades' chest physicians/physicians have increased awareness about the disease due to easy availability of immunodiagnostic tests, imaging modalities for diagnosis and potentially curable surgical and medical management of the disease. This study was carried out to confirm the demographic and clinical profile and various imaging features of the pulmonary hydatid disease described in literature and the outcome of treatment.

2. Material and methods

This retrospective observational study was conducted at a tertiary care center in Mumbai after ethics committee approval. Case records of patients with the diagnosis of pulmonary hydatid disease or pulmonary complications of hydatid disease involving other organs over a period of 10 years from 1997 to 2007 referred to the department of pulmonary medicine were reviewed. Demographic, clinical, radiological and laboratory data were collected and analyzed. Twenty seven patients were referred or attended for evaluation of imaging diagnosis of hydatid disease or suspected pulmonary complication of hydatid disease involving other organs. Out of the 27 patients, four patients were excluded. Three had liver hydatid cyst with simple pleural effusion and one with radiologic diagnosis of lung hydatid disease was found to have simple lung cyst on histopathology. Their demographic profile including name, age, sex, residence, occupation, clinical history involving details of symptoms, exposure to dogs was reviewed. Patients

were subjected to investigations which included chest radiograph posteroanterior and appropriate lateral view, complete blood counts including eosinophil counts and sputum for echinococcus granulosus. Serological test like indirect haemagglutination test was done in all except in initial 8 patients. Ultrasound examination of abdomen was done in all patients to look for liver involvement. Computed tomogram (CT) of thorax was done in majority (21 patients) with upper abdominal section for liver. ¹⁸F-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) imaging was performed in one case.

After clinical, radiological and serological evaluation and diagnosis; patients were referred to thoracic surgery department or pediatric surgery department of the institution for surgical treatment. All patients were given doses of albendazole pre and post operatively. Surgical specimen of cyst was sent to histopathological examination. Those who refused surgery or were inoperable were given medical therapy. Patients were followed up for 6 months to 3 years. Data collected was analyzed statistically in the form of frequencies and percentages.

3. Results

Twenty three patients were eventually included in this study. The mean age was 28.5 years with age groups ranging from 9 to 65 years. Fourteen (60.86%) patients were in the second and third decades (Table-1). Men outnumbered women consisting 73.91% and 26.09% respectively of the patient population (Table-2). Fourteen patients (60.86%) were hailing from rural regions. Fifteen patients (65.21%) had close contact with dogs. Twenty one patients (91.3%) were symptomatic and in 2 cases the findings were incidental. Cough was the most common symptom in 21 (91.3%), followed by hemoptysis (47.85%) and chest pain (43.47%). Salty taste of expectoration was noted in 7 (30.43%). The symptomatology is described in Table 3. A total of 34 cysts were present in these 23 patients. Right lung was involved in 16 cysts (47.06%) and left lung in 18 cysts (52.94%). The lobar distribution of 34 cysts is presented in table 4. Bilateral lower lobes had 19 cysts (55.88%) and were more involved than the upper lobes. Of all the lobes; right lower lobe was the most common site involved in 32.35% i.e. 11 cysts.

Chest radiograph showed a homogeneous round to oval opacity (Figure 1) in 18 cysts (52.94%), inhomogeneous opacity with irregular walls in 3 cysts (8.83%), cavity with air fluid in 3 (8.82%), water lily sign (Figure 2) and kissing cysts sign in 2 cysts each (5.88%). Rising sun sign, serpent sign (Figure 3), air crescent sign, coin lesion, solitary nodule, and large cyst with mediastinal shift were seen in 1(2.94%) each (Table 5). In the 23 patients, 13 (56.5%) had solitary lung cyst, 4 (17.4%) had unilateral multiple lung cysts, 5 (21.7%) had bilateral involvement and 1 (4.4%) had a posterior mediastinal cyst (table 6). Of the 34 cysts; 19 (55.89%) were

simple hydatid cysts and 15 (44.11%) were complicated cysts. CT thorax was done in 21 patients in whom total 32 cysts were reported (Table 7).

The most common presentations were iso to hypodense opacity with enhancing wall in 14 cysts (43.75%). Air specks in cysts and air fluid level were next common findings in 4 cysts each (12.5%). Whorled appearance, floating membrane, crescent sign, and mass in cavity were seen in ruptured cysts. Calcification was seen in none. Simultaneous involvement of liver and lung was seen in 8 patients (34.78%) and with spleen in one patient (4.34%). Cyst size ranged from 2.8 cms to 12.5 cms. Eosinophilia (> 4% or 400 per cubic mm) was seen in 8 (34.78%). Indirect haemagglutination test was done in 15 patients; with significant positive titer (> 1:320) in 9 (60%), indeterminate (1:160) in 3 (20%) and negative in 3 (20%). Skin testing was not done in this study. FDG PET/CT imaging was performed in one case and showed increased F-18 FDG tracer uptake along the cyst wall with central photopenia the "Doughnut sign" (Figure 4).

Fourteen patients were subjected to surgery and referred to thoracic surgery or paediatric surgery departments for the same. Total 20 cysts were removed surgically from these 14 patients. Excision of the cysts with capitonnage was the preferred technique done in 11 cysts (55%), others were excision of the cyst with bronchial fistula closure in 4 cysts and enucleation with capitonnage in one. Lung resection surgeries were done in ruptured cysts with adherent parenchyma in 4.

In these 14 patients, the surgical approaches adopted were as follows-1) Unilateral cysts were removed in a single staged operation, 2) Bilateral cysts were removed in two staged operation three weeks apart, 2) Simultaneous liver cyst was removed by transabdominal and transthoracic route in the same sitting in one patient, 3) Evacuation of liver cyst with closure of diaphragmatic rent was done in one, 4) The posterior mediastinal extension of liver cyst was dealt with transabdominal route, 5) Cyst rupture during hospitalization with increased cough and fever was dealt with emergency thoracotomy in one.

All patients were given pre and post operative dosage of albendazole to prevent recurrence from perioperative spillage. Post operative mortality was nil. Figure 5 represents the resected hydatid membrane. Two patients had empyema; while persistent air leak, hemorrhage, recurrent hemoptysis, residual cavity, bronchieactasis and recurrent cyst was noted in one each (Table 8). Medical treatment with albendazole (10 mg/kg/day) was given in rest 9 patients as they refused surgery or in whom cysts were inoperable or recurred. One recurrent ruptured cyst completely disappeared with medical therapy and rest either decreased in size. All patients were followed up for six months to three years without any mortality.

Table 1: Demography

Age Group	No. of Patients (N=23)	Percentage
0-10	1	4.34
11-20	8	34.78
21-30	6	26.08
31-40	4	17.39
41-50	2	8.69
51-60	1	4.34
61-70	1	4.34

Table 2: Sex Distribution

Sex	No. of Patients (N=23)	Percentage
Male	17	73.91
Female	6	26.09

Table 3: Clinical Presentation

Symptom	No. of Patient (N=23)	Percentage
Cough	21	91.30
Hemoptysis	11	47.82
Chest Pain	10	43.47
Salty Taste	7	30.43
Fever	7	30.43
Dyspnoea	4	17.39
Allergy	1	4.34
Expectoration of Cyst Content	1	4.34
Abdominal Pain	1	4.34
Asymptomatic	2	8.64

Table 4: Location of Cysts in Lung

Location		No. of Cysts (N=34)	%
Right Lung-16(47.05%)	Upper Lobe	3	8.82
	Middle Lobe	2	5.88
	Lower Lobe	11	32.35
Left Lung-18(52.94%)	Upper Lobe	6	17.64
	Lingula	4	17.39
	Lower Lobe	8	34.78

Table 5: Chest Radiography

CXR-Finding	No. of Cysts N=34	%
Homogeneous Round To Oval Opacity	18	52.94
Inhomogeneous Opacity With Irregular Wall	3	8.82
Kissing Cyst	2	5.88
Water Lily Sign	2	5.88
Air Crescent Sign	1	2.94
Coin Lesion	1	2.94
Air Fluid Level	3	8.82
Serpent Sign	1	2.94
Rising Sun Sign	1	2.94
Mediastinal Shift	1	2.94
Spn	1	2.94

Table 6: Distribution of Cysts

Location of Cysts		No. of Patients (N=23)	%
Unilateral-17 (73.91%)	Single	13	76.47
	Multiple	4	23.52
Bilateral-5(21.73%)	Single	3	60
	Multiple	2	40
Mediastinal	4.34%	1	-

Table 7: Computed Tomography (CT) of Thorax Findings

CT Thorax	No. of Cysts (N=32)	%
Iso To Hypodense Opacity With Enhancing Walls	14	43.75
Air Specks In Cavity	4	12.50
Cavity	2	6.25
Air Fluid Level	4	12.5
Floating Membrane	2	6.25
Air In Wall	1	3.12
Round Non Enhancing Wall	1	3.12
Mass In Cavity	1	3.12
Whorled Appearance	1	3.12
Extension In Post Med	1	3.12
Crescent Sign	1	3.12

Table 8: Post Operative Complications

Complication	No. of Patient (N=14)	%
Nil	6	42.85
Persistent Air Leak	1	7.14
Pleural Effusion/Empyema	2	14.28
Hemorrhage	1	7.14
Recurrent Hemoptysis	1	7.14
Residual Cavity	1	7.14
Bronchiectasis	1	7.14
Recurrence	1	7.14

Figure 1: The Chest X-Ray postero-anterior view showing a round to oval homogenous opacity



Figure 2: The Chest X-Ray postero-anterior and lateral view showing a cyst with an irregular air fluid level suggesting floating membranes known as the “Water-Lily sign”

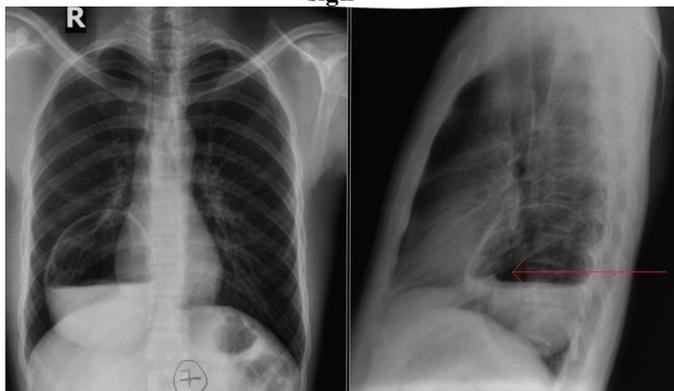


Figure 3: The high resolution computed tomography of thorax showing the folded membranes representing a snake known as the “Serpent sign”

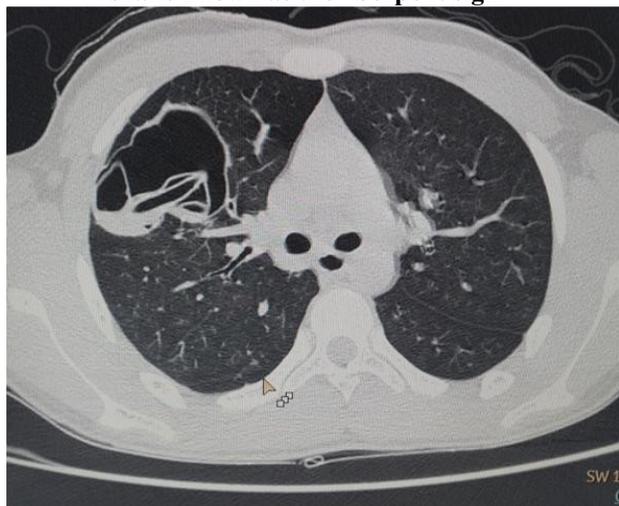


Figure 4: F-18 FDG-PET/CT showing a hydatid cyst with F-18 tracer uptake along the cyst wall with central photopenia known as the “Doughnut sign”.

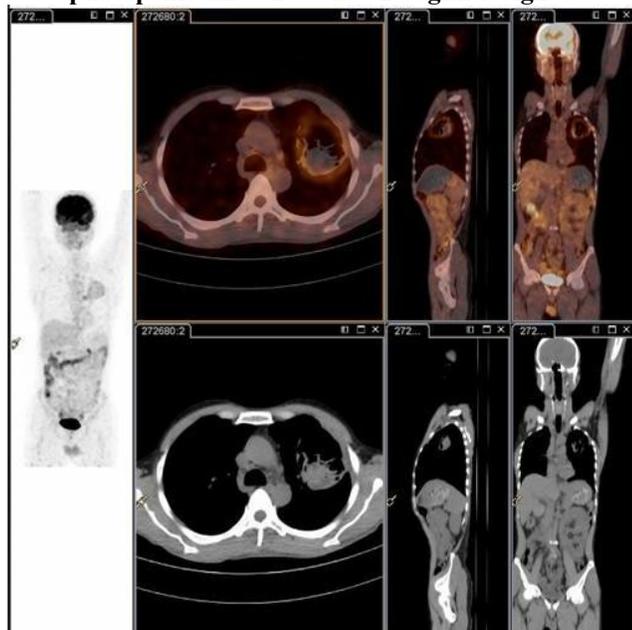


Figure 5: The image shows a resected hydatid membrane.



4. Discussion

Hydatid disease is worldwide in distribution and endemic in areas where sheep and cattle raising practices are common including India. The present study is a clinical study of hydatid disease in Mumbai, Maharashtra a non endemic area. It is evident from the present study that about 2-3 cases of hydatid lung disease involving the lung are seen every year even in a non endemic area as against studies from Wardha, Maharashtra which have reported a higher incidence.[2] It is common in rural population than urban dwellers[3-6]. In our study 60.86% (14 cases) were rural folks. Pulmonary hydatid cysts are equally common in men and women, in most series [3-9]. However, in our series male: female ratio was 2.83:1 which is similar to some series from India [4,6]. More than half of the patients (65.21%) had history of close contacts with dogs much higher than reported in literature [4]. Pulmonary hydatidosis can occur in any age group. It is known that most cysts are acquired during childhood but are not diagnosed until 3rd and 4th decade [3-9]. Liver is the most common organ involved in hydatid disease. However lung is the most common organ involved in children due to elasticity and compressibility of lung [5,7,8]. In our series 65.21% of patients were below 30 years and 39.13% below 20 years indicating an exposure at early age. Most common presentation of pulmonary hydatidosis is sudden coughing attacks followed by hemoptysis, chest pain, dyspnoea, salty taste due to rupture of cyst reported in most series, uncomplicated cysts may be asymptomatic in 5.35% cases [9-11]. In the present study, cough was the most common presenting symptoms in 91.3% followed by hemoptysis (47.82%) and chest pain (43.47%), and only in two patients (8.69%) hydatid cysts were incidental findings. On the contrary, Shehatha *et al* reported asymptomatic cysts in 37% of 763 cases.[12] Salty taste which is due to expectoration of cyst content was noted in 30.43% patient as against studies reporting it in upto 20% of patients[6,13]. Severe anaphylaxis

is uncommon however mild allergic reaction may occur [1], in our series one patient had mild urticaria, pruritus following rupture of cyst. Eosinophilia is non specific and is of little value in endemic areas where other helminthic infestations are common. It is reported in upto 15-50% of cases [4,6,9,14,15]. In our series eosinophilia $\geq 4\%$ or AEC $>400/\text{mm}^3$ was noted in 26.09%. Immunodiagnostic testing for serum antibodies or circulating antigen provides supportive evidence of pulmonary echinococcosis. Indirect hemagglutination (IHA) test is positive in only 50% patients with pulmonary hydatidosis and $\geq 90\%$ in hepatic cysts. A negative serological tests generally does not rule out echinococcosis and it is less likely to be positive if cysts are intact, calcified or non viable though positive tests help in the confirmation of diagnosis [14]. In our study, IHA was positive in significant titers in 60% cases. Skin testing is not reliable and does not give consistent results. Casoni's intradermal test is reported to be positive in 65% cases [4,13]; however in the present study such testing was not done.

Radiography is the mainstay to arrive at the diagnosis. Pulmonary hydatid cyst can be located in any pulmonary lobe. It is postulated that the right lower lobe is most frequently involved due to the abundance of pulmonary flow to this lobe [5,14]. According to most studies right lung is involved in 60%, multiple cysts occur in 30% and bilateral cysts in 20% cases and 60% cysts are located in lower lobes. Simultaneous involvement of liver is noted in 6-40% of cases [6,7,14]. In our study, the left lung was slightly more commonly involved in 52.44%, multiple cysts were seen in 26.08% patients, bilateral cysts in 21.73%, and 55.88% cysts were located in lower lobe. Liver was involved simultaneously in 34.78% and spleen in 4.34% patients. These findings were consistent with previous studies except left lung predominance seen in our study. Pulmonary hydatid cyst size ranges between 2-20 cm, and in the present study it was 2.8-12.5cm. CT thorax is useful for demonstrating the fluid density of cyst, identification of ruptured cysts, extent and localization of cyst and communication with other organs. Calcification of pulmonary hydatid cyst is rare occurring in 0.07% [16,17], none of our patients had calcification. The CT thorax showed communication of the liver cyst with the right middle lobe and extension of the liver cyst into the posterior mediastinum in one patient each. Percutaneous aspiration of lung cysts were deferred till recently due to fear of anaphylaxis, however Mc Corkell[18] described three cases of transthoracic aspiration without any adverse events. In this study one patient underwent CT guided diagnostic aspiration without any adverse events and microscopy showed hooklets and membrane consistent with hydatid disease. In the other USG guided aspiration, the patient had a mild allergic reaction. The utility of FDG-PET/CT in hydatid disease has been demonstrated in recent times. The "Doughnut sign" is described which is due to the F-18 FDG tracer uptake along the cyst wall with central

photopenia. Usually a complicated hydatid cyst, ruptured or infected or both are detected on FDG-PET or FDG PET-CT.[19] As this study was an analysis of records prior to 2007 this newer modality could not be performed in all cases.

Surgery is the definitive treatment for pulmonary hydatid disease with maximum chance of cure. Lung parenchyma preserving surgeries are preferred by most surgeons. Cystostomy with capitonnage, excision of cyst with capitonnage, pericystectomy, enucleation are the preferred surgeries by many surgeons. In this study excision of the cyst with capitonnage was the preferred surgery. No post operative mortality was seen. Post operative complications occurred in our series as shown Table-9. In most series mortality was ranged between 0-2% and recurrence rates from 0.5-11.3% were noted [7,20]. In our series only one recurrence of cyst was noted which was completely responded to medical therapy with albendazole. Albendazole in the dose of 10-15 mg/kg/d for 3-6 months without interruption shows decreased chances of recurrence¹. Simultaneous liver and lung cyst can be operated as one stage or two stage surgeries [21,-23]. Bilateral cysts can be managed with one stage operation through median sternotomy[21]. In the present study, bilateral cysts were operated in two stage surgeries with 3 weeks period in between as it is safer option and less morbidity compared to median sternotomy. Radical surgeries were done in 4 patients where surrounding lung parenchyma could not be separated due to intense adhesions. Medical treatment with albendazole (10 mg/kg/day) was given in 9 patients as they refused surgery or in whom cysts were inoperable or recurred. All showed good response to medical therapy with complete resolution or reduction in size of the cysts. Medical therapy is with benzimidazoles group of drugs (albendazole or mebendazole). Medical therapy is valuable in disseminated disease, including secondary lung or pleural hydatidosis and in poor surgical risk patients. The recommended dose of mebendazole is 40-50 mg/kg/day, given in three divided doses after meals (maximum daily dose 6 g). Albendazole is given at a dosage of 10-15 mg/kg/day in two divided doses and the usual dose is 800 mg daily. Therapy is most often indicated for a minimum of 3-6 months. Albendazole is preferred because it has better bioavailability.[24]

5. Conclusion

This study highlights the clinico-radiological profile and management options in pulmonary hydatidosis at a non endemic tertiary care center in Western India.

5.1 Clinical significance

Pulmonary hydatid disease is important public health problem of increasing concern in populations having close contact with dogs. So prevention through public health education is the most cost effective measure. Although the clinical picture is usually non specific, the clinical history is an important tool to suspect the diagnosis of pulmonary hydatidosis. Radiography assisted by serological testing in

appropriate clinical context helps to reach at the diagnosis. Simultaneous ultrasound or imaging studies of abdomen should be done to look for the concomitant cysts in the liver and other viscera in all patients with pulmonary hydatid cysts. Although surgical treatment is the definitive treatment with complete chance of cure and negligible mortality rates in experienced hands, medical therapy should be tried for recurrent cysts, multiple cysts, cysts involving multiple organs or in inoperable cases or in patients refusing surgeries and in patients having intra operative spillage. Lung preserving surgeries should be the preferred approach in all patients. Radical surgeries should be reserved for cases where irreversible lung damage has occurred. Close follow up of patient should be done to diagnose recurrences early in the course.

References

- [1] Sarkar M, Pathania R, Jhobta A, Thakur BR, Chopra R. Cystic pulmonary hydatidosis. *Lung India* 2016; 33:179-91.
- [2] Rao SS, Mehra B, Narang R. The spectrum of hydatid disease in rural central India: An 11-year experience. *Ann Trop Med Public Health* 2012; 5:225-30.
- [3] Zahirfard S, Karam MB, Kayanama K, Farzanegan R, Tahbaz MO, Abbasi A. Imaging in 100 patients of thoracic Hydatid disease including unusual imaging appearances. *Iran J Radiol Winter* 2006; 3(2):91-97.
- [4] Ayuso LA, Peralta GT, Lazaro RB, Stein AJ, Sanchez JA, Aymerich DF et al. Surgical treatment of pulmonary hydatidosis. *J Thorac Cardiovasc Surg.* 1981; 82:569-575.
- [5] Aytac A, Yurdakul Y, Ikizlea C, Olga R, Saylam A. Pulmonary Hydatid disease: report of 100 patients. *Ann Thorac Surg.* 1977; 23(2):145-151.
- [6] Rai SP, Panda BN, Ganguly D, Bharadwaj R. Pulmonary Hydatid: diagnosis and response to hypertonic saline irrigation and albendazole. *MJAFI* 2005; 61(1): 9-12.
- [7] Tor M, Atasahili A, Altuntas N. Review of cases with cystic Hydatid lung disease in a tertiary referral hospital located in an endemic region: a 10 years experience. *Respiration* 2000; 67; 539-542.
- [8] Aribas O K, Kanat F, Gormus N. Pleural complication of Hydatid disease. *J Thorac Cardiovasc Surg.* 2002; 123(3); 492-497.
- [9] Dogan R, Yuksel M, Cetin G, Suzer K, Alp M, Kaya S et al. Surgical treatment of Hydatid cysts of the lung: report of 1055 patients. *Thorax* 1989; 44: 192-199.
- [10] Sarsam A. Surgery of pulmonary Hydatid cysts review of 155 cases. *J. Thorac Cardiovasc Surg* 1971; 62(4):663-668.
- [11] Hacıbrahimoglu H, Celik M, Senol C, Alpay O, Urek S, Arman B. Surgical treatment of complicated cysts of the lung. *Turkish Respiratory Journal* 2003; 4(3):127-130.
- [12] Shehatha J, Alizzi A, Alward M, Konstantinov I. Thoracic hydatid disease; a review of 763 cases. *Heart Lung Circ* 2008; 17:502-4.
- [13] Maniar D R, Iyer R K, Joshi J M. Pulmonary hydatidosis: medical and surgical management. *JAPI* 1996;44(1); 63-64.
- [14] Beggs I. The radiology of Hydatid disease. *AJR* 1985; 145:639-648.
- [15] Sharma S K, Eggleton F C. Management of Hydatid disease. *Arch Surg* 1969; 99:59-63.
- [16] Pedrosa I, Sair A, Arrazola F, Ferreiros J, Pedrosa CS. Hydatid disease: radiologic and pathologic features and complication. *Radiographics* 2000; 20(3); 795-817.
- [17] Walther Von Sinner. Advanced medical imaging and treatment of human cystic echinococcosis. *Seminars in roentgenology* 1997; 32(4): 276-290.
- [18] Mawhorter S, Temeck B, Chang R, Pass S, Nash T. Nonsurgical therapy for pulmonary Hydatid cyst disease. *Chest* 1997; 112:1432-1436.
- [19] Shekhar G, Kadam, Sandip Basu, J.M. Joshi. Doughnut Sign on FDG-PET Scan in a Ruptured Lung Hydatid Cyst. *Indian J Chest Dis Allied Sci* 2012; 54:185-187.
- [20] Yalcinakaya F, Er M, Orbay B, Ugras S. Surgical treatment of Hydatid cyst of the lung: review of 30 cases. *Eur Respir J* 1999; 13:441-444.
- [21] Biswas D, Ghosh D, Bhattacharjee R, Patra A, Basuthakur S, Basu R. One stage bilateral thoracotomy for Hydatid cysts of both lungs. *IJTCVS* 2004; 20:126-128.
- [22] Xanthakis DS, Katsaras E, Efthimiadis M, Papadakis G, Varouchakis G, Aligizakis C. Hydatid cyst of the liver with intrathoracic rupture. *Thorax* 1981; 36:497-501.
- [23] S.Bhat, Kamble R T, Sundaram P, Joshi J M. Transdiaphragmatic extension of hepatic Hydatid cyst. *Indian J Chest Dis Allied Sci.* 2002;44; 191-194.
- [24] Anadol D, Ozcelik U, Kiper N, Gocmen A. Treatment of hydatid disease. *Paediatr Drugs* 2001; 3:123-135.