Clinico-pathological profile of solitary pulmonary nodule presenting to a tertiary care hospital-a cross sectional study

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Abstract

Background: The diagnosis, classification and management of a solitary pulmonary nodule (SPN) have always been a challenge for the clinicians and radiologists. All SPNs should be considered malignant until proven otherwise. Malignancy risk rises with increasing nodule size. Hence evaluation of the various clinical and pathological presentations of SPN is essential.

Methodology: A hospital-based cross-sectional study was conducted in a tertiary care teaching hospital on 70 cases of SPN. Chest X-ray, CT (Computed Tomography) and bronchoalveolar lavage were used for analysing the SPN. IBM SPSS version 22 was used for statistical analysis.

Results: The incidence of SPN in this study was 1.33 per 1000 population. The total number of chest X-rays screened were 5263. The most common risk factors were exposure to PTB (Pulmonary Tuberculosis) or history of PTB (97.1%), followed by smoking (81.4%), history of STD (32.9%). Dry cough was the most common symptom among (20%). In X-ray, in 57.1% of subjects, the upper lobes were involved. Lesions were central in 41.4% while peripheral in 58.6%. The proportion of nodules with 1.1 to 2cm and above 2 cm was 22.85% and 77.15%. No calcification was found in 78.6% of nodules. In SPN the most common final diagnosis was tuberculosis (14.3%) followed by Pneumonia/abscess (8.6%) and Squamous cell carcinoma and Pseudotumor (5.71% each). 20% of SPN were malignant. 11.42% of nodules turned out to be primary lung malignancy while 1.42% were metastasis and 7.1% were small cell carcinoma.

Conclusions: SPN is a common incidental and radiologic finding. Some internal features of SPNs can help in differentiating benign from malignant lesions. Despite radiological imaging, still, a large number of nodules have to be described as "indeterminate" and advanced and often more invasive techniques are needed for further work-up.

Keywords: Solitary pulmonary nodule (SPN); Malignancy, Incidence; Bronchoalveolar lavage.

Introduction

The diagnosis, classification and management of a solitary pulmonary nodule (SPN) have always been a challenge for the clinicians and radiologists. Nowadays, pulmonary nodules are detected more often than normal, with numerous lesions being difficult to be classified as benign or malignant. "A Solitary pulmonary nodule is defined on imaging as a small, well-defined lesion no larger than 3 cm and is surrounded by normal functioning pulmonary parenchyma in the absence of atelectasis, hilar enlargement and pleural effusion" [1-3]. According to the radiological definition of Fleischner Society SPN is around opacity which is moderately well-marginated with a maximum diameter of 30 mm [4]. They are round or egg-shaped lesions in the lungs which are typically asymptomatic.

They are usually detected on a chest x-ray done for other clinical reasons posing a diagnostic dilemma for clinicians. Their differential diagnosis may range from infective, inflammatory causes to vascular, traumatic and congenital causes [5]. They can also be categorised as benign or malignant lesions. Lesions which are more than 3 cm are considered masses and not nodules as the likelihood of malignancy is high in them, and they are dealt with differently. In India, up to sixty per cent of all SPNs could be benign due to the high rate of infections specially TB. The risk of malignancy rises with increasing nodule size. Approximately 80% of nodules greater than 20 mm are malignant, whereas only 1% of nodules between 2 and 5 mm are malignant [6]. Malignant solid nodules typically have a doubling time within 400 days. The economic and health burden caused by lung cancer in society is enormous. It is the most commonly diagnosed cancer apart from keratinocyte carcinoma and is the greatest cause of cancer-related death [7]. Malignant SPNs may be primary stage IA lung cancer or metastases.

Up to 30% of all bronchogenic carcinoma can present as SPN [5,8]. Unfortunately, approximately one-half of all lung cancers have extrapulmonary spread at the time of diagnosis. As a result, the average patient with a diagnosis of lung cancer has a five year survival of only 10 to 15% [9]. Therefore, it is prudent that the malignant form of SPN is promptly evaluated and managed [10]. In general, all SPNs until they are proved otherwise, should be considered malignant. Also, a confirmed diagnosis of benign lesions like infections including TB, granulomata and benign lung tumor also can avoid the unnecessary exploratory thoracotomy with its attendant morbidity. Cases of bronchogenic carcinoma also have an excellent 5-year survival rate when diagnosed early [11]. So we evaluated the various clinical and pathological presentations of SPN in a tertiary care center in Andhra Pradesh.

Materials and Methods

This is a study of 70 cases of Solitary Pulmonary Lesion presented at Katuri Medical College and Hospital, a tertiary care hospital in south India. An written informed consent from study subjects was obtained.

Type and Period of Study

This study was done from August 2016 to December 2018 **Setting**

A single discrete pulmonary opacity surrounded by normal lung tissue and not associated with adenopathy/atelectasis in the chest X-ray in the following group of fifty adults was taken as the starting point of the study. To overcome observer bias, the concurrence of four individual observers was taken as a pre-requisite to include the case in the study population. **Study Population**

Asymptomatic adults, who had undergone hospital run master health checkup programme. Patients presented with chest symptoms in medicine OPD, Individuals who presented themselves for unrelated complaints in different OPDs for whom a routine chest X-ray was called for.

Inclusion Criteria

Following X-ray findings were taken as criteria for inclusion of subjects:

- A. Cases presenting with solitary pulmonary parenchymal nodular lesion of 1-3 cm in diameter.
- B. The nodule appears to lie within the pulmonary parenchyma, with aerated lung tissue around it.
- C. The lesions are round or ovoid.
- D. Patients may have associated minimal pneumonitis, atelectasis or regional lymphadenopathy.
- E. The lesions are solitary (in some cases satellite lesions may be present) with circumscribed margin.

Exclusion Criteria

Size of the nodule >3cm; Obvious hilar, mediastinal, diaphragmatic and chest wall masses; co-morbid conditions; bleeding diathesis– as assessed by BT, CT, platelet count Pulmonary hypertension Multiple bullous lesions Extremely sick/dyspnoeic patient

Method

Detailed history with special reference to age, sex, smoking history, exposure to TB / STD, occupational risk and exposure to asbestos, nickel, chromium, polycyclic hydrocarbon, previous history of TB / pulmonary mycosis, DM, immune suppressive disease/drugs were obtained. A thorough clinical examination with special attention to the respiratory system, para-neoplastic syndromes and signs of metastasis was done. All other systems, especially, GI tract, prostate, testis, kidney, thyroid and breast & pelvis in females were carefully examined for primary lesion. Other than routine blood, urine, tuberculin test, other important investigations were also done. Sputum-Gram stain, AFB stain, fungal KOH stain, bacterial C/S, mycobacterium TB Culture- L-J medium or Liquid culture medium, fungal culture in labour and agar medium, malignant cell examination was done. Chest X-ray – PA view mostly, with an occasional lateral view and digital enhancing X-ray as needed- the size of the lesion, growth rate, margin characteristics, calcification pattern were looked into for assessment and differentiation between benign/infective/ malignant lesions. Better visualisation and appreciation of nodule/mass is possible in CT thorax. No. and size, calcification pattern, staging for malignancy, densitometry of lesion, contrast enhancement, wall thickness, and positive vessel sign was noted for differentiation between benign/infective/ malignant lesions. CT guided percutaneous fine needle aspiration cytology / true-cut needle biopsy – from peripheral lesions and histopathological examination of the same. Broncho-alveolar lavage, brushing, bronchoscopic biopsy for centrally placed lesions were done with a bronchoscopy. Fine needle aspiration cytology/excision biopsy of palpable significant lymph nodes, if any were done.

Results

A total of 5263 x-rays were screening during the study period, and 70 cases of solitary pulmonary nodule were diagnosed. Hence the Incidence of SPN in this study is 1.33/1000 population.

Parameter	Number of case	Percentage	
Age group (years)			
20-30	3	4.28%	
31-40	10	14.28%	
41-50	28	40.00%	
51-60	25	35.71%	
60 and above	4	5.71%	
Gender			
Male	66	94.28%	
Female	4	5.71%	

 Table 1: Descriptive analysis age and sex distribution

The mean age was 54.3 years. The majority (40%) of the participants were aged between 41 to 50 years. The proportion of subject aged between 51 to 60 years and 31 to 40 years age group was 35.71% and 14.28% respectively. Males and females constituted 94.28% and 5.71% of cases. (Table 1)

Table 2: Risk factors and clinical presentation of the solitary pulmonary nodule cases among the study population (N=70)

Parameter	No. of patients	Percentage	
Risk factors			
Exposure to or past h/o PTB	68	97.1	
Smoking	57	81.4	
History STD exposure	23	32.9	
Occupational exposure	13	18.6	
Diabetes mellitus	11	15.7	
Immunosuppressive Drugs	4	5.7	
No risk factor	7	10.0	
Clinical symptoms			
Asymptomatic	25	35.7	
Dry cough	14	20.0	
Cough + Expectoration	8	11.4	
Mailse/easy fatigability	8	11.4	
Chest pain	7	10.0	
Cough + Dyspnea	3	4.3	
Cough + Hemoptysis	2	2.9	
Loss of weight	3	4.3	

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Duration (months)				
Asymptomatic	25	35.7		
$0 - \frac{1}{2}$	21	30		
¹ / ₂ - 1	11	15.7		
1 – 2	6	8.6		
2-3	3	4.3		
3 and above	4	5.7		
Physical signs				
No sign	18	25.7		
Cervical	7	10.0		
lymphadenopathy	1	10.0		
Clubbing	8	11.4		
Hepatomegaly	1	1.4		
Skin nodule	2	2.9		
Minimal lung signs	35	48.6		

The most common risk factor was exposure to TB or a history of PTB (97.1%), followed by smoking (81.4%), history of STD (32.9%). Occupational exposure to dust and other pollutants was reported by 18.6% of the subjects. The other common risk factors being, diabetes mellitus, immunosuppressive therapy. No risk factors were reported by 7 (10%) subjects. Among 35.7% of participants, the SPN was detected accidentally. Dry cough was the most common symptom among 20%, followed by productive cough among 11.4% of subjects. Among the people with physical signs, the majority (48.6%) participants had minimal lung signs, and 25.7% had a normal physical examination. Clubbing was seen in 11.4% of participants. (Table 2)

Analysis of Duration of Symptoms: (Table 4, Chart 4)

Among the symptomatic cases, the interval between the onset of symptoms and seeking consultation was 15 days in 21 (30%) patients, 16 days to 1 month in 11 (15.7%) and 1-2months in 6 (8.6%). This pattern suggests that there is a high probability that SPN may be present sub-clinically in more than one third of cases and when symptoms occur, majority patients are likely to seek care within the first month. (Table 2)

Table 3: Location of the solitary pulmonary nodule on Chest

 X-ray (N=70)

Site		No. of cases	Percentage
Upper Lobe	right	22	31.4
Opper Lobe	left	18	25.7
Middle Lobe	right	3	4.28
	left	1	1.42
Lower Lobe	right	17	24.28
	left	8	11.42

From the above table, it is evident that in more than half of the total cases (57.1%), the upper lobes were involved. The right-side involvement was more, i.e. in 42 out of 70 (60%) cases. Central lesions were 29 (41.4%), and peripheral lesions were 41 (58.6%).

Table 4: Summary of Radiological and other investigation
findings as assessed by CT examination (N=70)

Computerised Tomography findings	No. of patients	Percentage	
Size in cm			
1.1 - 2	16	22.85	
2.1 – 3	54	77.15	
Margin characteristics			
Smooth	38	54.3	
Lobulated	7	10.0	
Spiculated	25	35.7	
Thickness of cavity			
Non – cavitary	61	87.1	
< 4 mm	4	5.7	
4 – 15 mm	3	4.3	
> 15 mm	2	2.9	
Calcification pattern			
No calcification	55	78.6	
Benign pattern	13	18.6	
Stippled / eccentric	2	2.9	
Contrast enhancement			
< 15 HU	25	35.7	
> 20 HU	45	64.3	

The proportion of nodules with 1.1 to 2cm and above 2 cm was 22.85% and 77.15%. Analysis margin characteristics by CT showed that the majority (54.3%) participants had a smooth margin. The speculated margin was observed in 35.7% of participants. The majority (87.1%) of the nodules were non-cavitary. In the remaining the thickness of cavity was <4mm among 5.7%, 4.3% of participants had 4 to 15 mm. No calcification was found in 55 (78.6%) of the subjects, benign and stripped/eccentric pattern of calcification was observed in 18.6% and 2.9% of the cases respectively. On contrast enhancement assessment, 25 (35.7%) participants had <15 HU and 45 (64.3%) participants had >20HU. Among 7 people, who underwent lymph node biopsy, 4(57.1%) had squamous cell carcinoma, 2(28.6%) had small cell carcinoma and 1 914.2%) had metastasis. Among 31 people undergoing transthoracic needle aspiration cytology/biopsy, unspecified malignancy was the most common lesion (32.3%), with adenocarcinoma as the most common variety. The other common findings were inflammatory cytology, tuberculosis and sarcoidosis. Among 21 subjects undergoing Fibreoptic Bronchoscopy 4 (19%), each had unspecified malignancy, tuberculosis and nonspecific cytology. (Table 4)

Diagnosis	No. of cases	Percentage
Primary lung Malignancy	8	11.42
Squamous cell carcinoma	4	5.71
Adenocarcinoma	2	2.85
Small cell carcinoma	1	1.42
Metastasis	1	1.42
Tuberculosis	10	14.3
Pneumonia / abscess	6	8.6
Small cell carcinoma	5	7.1
Pseudotumor	4	5.71
Mucoid impaction	3	4.3
Carcinoid	2	2.8
Benign tumor – hamartoma	2	2.9
Sarcoidosis	2	2.9
No definite diagnosis	27	38.57

Table 5: Final diagnosis of a solitary pulmonary nodule inthe study population (N=70)

Among the people with the solitary pulmonary nodule, the most common final diagnosis was tuberculosis among 10 (14.3%) participants, followed by Pneumonia/abscess was 8.6% and Squamous cell carcinoma and Pseudo –the tumor was 5.71%, each respectively. (Table 5)

 Table 6: Diagnostic yield of various investigations in the diagnosis of SPN

Basis of Diagnosis	No. of cases effective	Total no. of cases	Percentage
Sputum for AFB	5	70	7.14%
Sputum for malignant cells	3	70	4.28%
Sputum culture / sensitivity	5	70	7.14%
Lymph node aspiration cytology / excision biopsy	7	7	100%
Transthoracic aspiration cytology / biopsy	26	31	83.87%
Fibre – optic bronchoscopy lavage / brushing / biopsy	18	21	85.71%
CT scan with contrast	5	70	7.14%

Out of the 5 cases (2 cases of transthoracic needle aspiration/biopsy, other 3 of bronchoscopy biopsy) of indefinite diagnosis of non–specific cytology, 2 cases were reasonably proved to be a benign lesion. Both of them were 2 cm, smooth margin nodule, and were males in the age group of 36–45yrs. Both these nodule sizes remained the same over 1-year period of follow–up. Other 3 cases are on follow–up currently.

Discussion

The incidence of SPN in this study was 1.33 per 1000 population. The total number of chest X-rays screened were 5263. The incidence of lung cancer in India and Central- and West-Africa was reported to be low on comparison with other regions of the world with 0.9-10/100,000 men and 0.6-2.3/100,000 women [8,12]. "An accepted definition of solitary pulmonary nodules (SPNs) is a single, clearly defined, radioopaque lesion in the lung surrounding entirely by air-containing lung tissue, in a diameter less than or equal to 3 cm, without atelectasis, hilar enlargement or pleural effusion" [1-3]. The detection of nodules has increased in the recent decades with advancements in Computed Tomography (CT). Generally, to be found on a chest X-ray, a pulmonary nodule must grow to a diameter of at least 1 cm. The detection rate of an SPN is 0.09% to 7% on routine chest radiographs [13]. On CT scans the screening prevalence of at least one SPN is higher ranging from 8% to 51% [8]. The prevalence of malignancy in single pulmonary nodules reflects their incidences ranging from 1% to 12% in the various studies [14,15]. Multiple pulmonary nodules are, on occasion, also encountered incidentally. In this setting, the diagnostic evaluation refers to the predominant type or the most suspicious nodule. Pulmonary nodules may be detected on cross-sectional imaging studies performed for an unrelated reason (i.e., incidental pulmonary nodule). A total of 70 subjects with SPN were included in the study with the majority (94.28%) of them being males. The Mean age was 54.3 years with the majority (40%) in the age group of 41 to 50 yrs. With regards to the baseline risk profile of the study population, 81.4% of the subjects were smokers while 97.1% had a history of exposure to Tuberculosis cases. 32.9% had a history of exposure to STD. Risk factors indicating a high probability of malignancy as studied by Goo et al., [16] include COPD, smoking history, and history of asbestos exposure besides the size of the nodule, age and history of the tumor.

The majority were chest asymptomatic (36%). Commonest symptoms were dry cough (20%, cough with expectoration (11.4%). Among the people with physical signs, the majority (48.6%) participants had minimal lung signs, and 25.7% had a normal physical examination. The major question that follows the detection of a pulmonary nodule is the probability of malignancy, with subsequent management varying accordingly. SPNs can be either benign or malignant. Their most common causes include infections and local inflammation. They often represent the lung malignancies, particularly small adenocarcinoma and [10]. bronchoalveolar carcinoma However. the distinguishment between benign and malignant SPNs and their treatment remain a hot and challenging research topic. The proportion of nodules with 1.1 to 2 cm and above 2 cm was 22.85% and 77.15%. Lesions which are more than 3 cm are considered masses and not nodules as the likelihood of malignancy is high in them, and they are dealt with differently. In India, up to sixty per cent of all SPNs could be benign due to the high rate of infections especially TB. The risk of malignancy rises with increasing nodule size.

Approximately 80% of nodules greater than 20 mm are malignant, whereas only 1% of nodules between 2 and 5 mm are malignant [6]. 48.6% of subjects had nodules in the size of 1 to 6 cm. Generally, small nodules tend to be benign, while larger ones are more likely malignant. The probability of malignancy is less than 1% in nodules <4 mm, and around 0.9%, 18% and 50% in those of 4-7 mm, 8-20 mm and 20-30 mm, respectively. Therefore, the SPN diameter can be used as an independent risk factor for differentiating malignant and benign lesions. Approximately 80% of nodules greater than 20 mm are malignant, whereas only 1% of nodules between 2 and 5 mm are malignant [6]. The 2013 ACCP guidelines for the evaluation of the solitary pulmonary nodule recommend basing the assessment on nodule size and the probability of malignancy [5]. 54.3% of nodules in this study had smooth margins while in 35.7%, the nodules were speculated. No calcification was found in 78.6% of subjects. The benign and stripped/eccentric pattern of calcification was observed in 18.6% and 2.9% of the cases respectively. The risk of malignancy is also higher in spiculated lesions, in lesions with asymmetric calcification, and lesions located in an upper lobe.6 In contrast, nodules with smooth borders and a central or concentric pattern of calcification are more likely to be benign. Calcification in an SPN on imaging indicates a high probability that the lesion is benign [17]. Six different patterns of calcification have been described in the literature. They are "(1) central dense nidus, (2) diffuse solid, (3) laminated, (4) popcorn, (5) punctuate, and (6) dendriform" [17]. Calcifications of diffuse, central, laminated, or popcorn type are usually benign and are commonly seen in granulomas and pulmonary hamartomas while other patterns should not be considered as benign. 20% of nodules turned out to be malignant in our study. Siegelman SS et al., [18] in their study observed that benign nodules made up 44% of all SPN. All malignant SPNs were assessed as indeterminate, and adenocarcinoma (42%) was the most common primary malignancy. In the study done by Colice et al., [19], benign and malignant SPNs accounted for 97% and 3%, respectively, in 504 patients with calcified nodules, and 29% and 71% in 1,109 patients without calcification, respectively. Zwirewich et al., [20] in their study, observed that malignant nodules as a group were larger than benign lesions (P = .02) and more commonly demonstrated a spiculated contour (P less than .05), lobulation (P less than .001), and inhomogeneous attenuation (P less than .05). In more than half of the total cases in our study (57.1%), the upper lobes were involved. The right-side involvement was more (60%). In 41.4% of subjects, the location of SPN was central while in 58.6%, it was peripheral. The majority (87.1%) of the nodules were non-cavitatory in this study. In the remaining, the thickness of the cavity was <4mm among 5.7%, 4.3% of participants had 4 to 15 mm. The nodules with thin walled cavities are more likely to be benign while a thick-walled cavity (>15 mm) is typical of a squamous cell carcinoma but could also be seen in TB cases or aspergillomas. Lung cavities are not as often seen in small lung cancer as tuberculoma. A cavity in lung cancer is mostly eccentric with uneven wall thickness. On contrast enhancement assessment.

25 (35.7%) participants had <15 HU and 45 (64.3%) participants had >20HU. Swensen et al., [21] found that nodule enhancement <15 HU is strongly predictive of benignity. With 15 HU as the threshold, the sensitivity for detecting malignancy was 98%, for detecting specificity was 58%, and for detecting accuracy was 77%. Among the symptomatic cases, the interval between the onset of symptoms and seeking consultation was 15 days in 30% subjects and 15 to 30 days in 15.7%. This pattern suggests that there is a high probability that SPN may be present subclinically in more than one third of cases and when symptoms occur, majority patients are likely to seek care within the first month. 11.42% of nodules turned out to be primary lung malignancy in our study while 1.42% were metastasis and 7.1% were small cell carcinoma. In primary lung malignancy, 5.71% were squamous cell carcinoma, 2.85% were adenocarcinoma, and 1.42% were small cell carcinoma. In SPN the most common final diagnosis was tuberculosis (14.3%) followed by Pneumonia/abscess (8.6%) and Squamous cell carcinoma and Pseudotumor (5.71% each). When a SPN is ≤ 2 cm in diameter, especially located in the outer 1/3 field of the lungs, its diagnostic accuracy is merely 14%.22. The development of endobronchial ultrasound, ultrathin bronchoscopy and electromagnetic navigation has improved the sensitivity of TBLB. Siegelman et al., [18] in their study observed that a total of 176 (63% of benign SPNs) were correctly assessed as benign by CT, but in our study, CT scan with contrast was effective only at a level of 7.14%. Highest accuracy was seen with Fibreoptic bronchoscopy lavage /brushing/biopsy (85.71%) and transthoracic aspiration cytology/biopsy (83.87%).

Generally, nodular opacities with greater than 3 cm diameter, also known as lung masses have a much higher probability of being malignant [23] while the smaller lesions (<2 cm diameter) tend to be benign.24 Some of those nodules with a diameter equal to or even less than 1 cm are malignant lesions detected in their earlier stages [15]. But the positive relationship of the lesion size to the likelihood of malignancy has been proved in studies [25]. Benign lesions are more likely to have smooth, well-marginated borders while on the other hand malignant nodules usually have ill-defined, irregular or lobulated contours [26]. But still, there is a significant overlapping between these findings. Nodules with spiculated borders (due to malignant cells extending within pulmonary interstitial tissue) sometimes termed as a "corona radiata" or "sunburst" are highly suspicious for malignancy, but the similar appearance can also represent benign infectious/inflammatory lesion [26].

This study was only a simple descriptive study with a small sample size to put forward the hypothesis about SPN and its risk factors and clinical presentation. Further exploratory and analytical studies are the need of the hour.

Conclusions

SPN can be of varied etiologies ranging from infections, connective tissue disorders, benign and malignant neoplastic conditions. There is no one single correct approach for the diagnosis, and hence the workup can be extensive. The current role of diagnostic imaging is to differentiate malignant lesions from more benign causes. However, despite some features that can help with this differentiation, still a large number of nodules have to be described as "indeterminate" and advanced and often more invasive techniques might be needed for further work-up.

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