Bronchopulmonary Candidiasis: Clinical Aspect

S. C. Chakravarty, M.B., F.C.C.P.
Delhi, India

In a recent survey, Chakravarty and Sandhu found 37 per cent of bronchopulmonary candidiasis patients had chronic bronchitis, bronchiectasis, and chronic pulmonary disease. The most common presenting symptom was a persistent cough, which was accompanied by phlegm with a mucoid or purulent appearance. The cough was often accompanied by wheezing and breathlessness.

The clinical diagnosis of bronchial candidiasis is not easy. The clinical presentation may include cough, fever, and purulent sputum. The most accurate criterion for diagnosis is the presence of Candida in sputum. However, the clinical picture may be indistinguishable from other forms of bronchial disease.

Criteria for clinical diagnosis of bronchial candidiasis:

1. Sputum should be positive for Candida species, as stated by Chakravarty and Sandhu, after at least four times for C. albicans, or one lysis of the following clinical findings:
   a. Positive culture for Candida species
   b. Positive smears for Candida species
   c. Positive antigen detection for Candida species
2. The patient may have more than one of the following clinical findings according to the state of the disease:
   a. Positive culture for Candida species
   b. Positive smears for Candida species
   c. Positive antigen detection for Candida species
3. When bronchoscopy can be done, bronchoalveolar lavage should be positive for Candida species.
4. When bronchoscopy cannot be done, bronchial aspirate should be positive for Candida species.

The radiologic findings of bronchial candidiasis include:

a. A widespread radiologic pattern of lung, with a predilection for lower lobes
b. A widespread radiologic picture of lung, with a predilection for lower lobes

The roentgenologic finding may be present in cases of bronchial candidiasis, but no in cases of bronchial candidiasis.
where only peribronchial thickening may be present.

5. After treatment with specific antifungal drugs, independent of other drugs, patient will improve.

All the cases diagnosed clinically as bronchopulmonary candidiasis in this series were according to the above criteria. In all, 11 patients were diagnosed as having bronchopulmonary candidiasis, but only nine patients received antifungal treatment including one patient of primary pulmonary candidiasis.

Patients were treated with either oral nystatin tablets or with oral nystatin tablet along with aerosol of suspension of nystatin. Each nystatin tablet is equivalent to 500,000 units. Four patients got only nystatin tablets orally and five patients received it both orally and by aerosol.

Nystatin tablets were given orally, one tablet four times daily for two to three weeks. Aerosol suspension of nystatin in 40 per cent propylene glycol, 50,000 units daily in four divided doses was given.

Total number of tablets received by patients were 56-92 tablets.

Methods for preparation of suspension of nystatin for aerosol and the mode of giving aerosol therapy:

A suspension of nystatin in 25 per cent ethanol in saline was used previously by us for aerosol therapy, but for the last two years, nystatin suspension in 40 per cent propylene glycol in normal saline is used, as it is found superior in action to the former.

Sixteen mg of sterilized nystatin powder with potency of 3150 units/mg are added to propylene glycol and normal saline is added to bring down the concentration of the suspension to 40 per cent.

It contains 4 mg (12,600 units) of nystatin per ml of suspension. Size of the particles are measured. Size of 90 per cent of the nystatin powder particles are less than 3 μg and five per cent are 3 to 5 μg and the rest are above 5 μg.

The suspension is shaken each time before using as aerosol. Aerosol therapy can be given with intermittent positive pressure breathing in inspiration for wider penetration of drugs in the lung. The pressure is kept between 10-15 cm of water.

Aerosol can also be given by hand nebulizer. Total amount of nystatin to be given depends on the degree of lesion in lungs. Four divided doses of 25,000 units to 50,000 units are given daily. Higher concentration of the suspension may also be given if necessary.

Observations

A total of 11 patients were diagnosed as having bronchopulmonary candidiasis. One patient had pulmonary and ten had bronchopulmonary candidiasis. One patient was of primary type and the other patients had secondary bronchopulmonary candidiasis.

Of the secondary bronchopulmonary group, nine had chronic bronchitis with emphysema and one had bronchiectasis.

All the patients received two to three antibiotics for ten days to 30 days before they had bronchopulmonary candidiasis. Only four patients received steroids for seven-18 days along with antibiotics.

Roentgenologic Appearance

Roentgenologic appearance was not of diagnostic significance, but in three patients after treatment with nystatin, hazy areas on roentgenogram cleared.

Bronchial biopsy was done only in four patients. Yeast cells were identified in bronchial tissue.

Results and Treatment

All nine patients improved clinically with nystatin and resumed their usual occupation. They occasionally coughed and expectorated due to their primary disease.

Four patients were treated only with oral nystatin tablets. All of them improved clinically, but sputa of only two patients became negative for Candida albicans and in other two patients, culture of sputum did not become negative and showed scanty growth. Culture became negative after nystatin aerosol was given in these two patients.

All the five who received nystatin aerosol along with oral nystatin tablets, im-
proved clinically and sputum of all of these patients became negative for C. albicans.

ILLUSTRATIVE CASE REPORT

A 50-year-old man was referred to Vallabhbai Patel Chest Institute Clinical Research Centre from Bilai in Madhya Pradesh in India.

When he was first seen in this clinic on October 4, 1965, he was very weak, ill-looking, dyspneic and was brought in a stretcher. He had intermittent rise of temperature up to 101°F. He had no appetite and could not sleep for about two weeks. He had cough with scanty expectoration of mucoid type. He lost about 18 pounds of body weight in three months.

PAST HISTORY

The patient is an engineer. In October, 1964, he worked in a place where he had to inhale dense diesel fumes for ten days. He started having cough with scanty expectoration and difficulty in breathing. He got relief after a course of autovaccine in May, 1965 and was feeling better though weak and lethargic. In June, 1965, he was examined at Chandigarh where he was pronounced normal except for his nasal polyp. On July 5, 1965, he drove to Bilai from Chandigarh by car and felt fatigued by the strain of journey. On July 10, 1965 he began experiencing rise of temperature up to 101°F off and on. He became weak, started losing weight, and had cough with scanty expectoration and night sweats.

Roentgenologic examination of the chest showed radiopacity of upper and midzone of the right lung.

Sputum was negative repeatedly in smear and culture for acid-fast bacilli and also for malignant cells. Erythrocyte sedimentation rate was 5 mm (Westergren) in first hour. However, the patient was given streptomycin injection 1 gm daily and isonicotinic acid hydrazid 300 mg. Within a week, the patient felt better symptomatically and roentgenologic appearance of lung showed clearing on right side.

While on antituberculosis regimen, his fever subsided and he again started coughing, had night sweats and became weaker.

Roentgenologic examination of the chest at this time showed reappearance of hazy shadows in right lung which extended down to the lower zone and also upper zone of left lung.

Hemogram showed leukocytosis of 19,300 per mm³, polymorphonuclears 72 per cent, erythrocyte sedimentation rate 123 mm (Westergren). Blood culture for bacteria was sterile. Repeated sputum culture for bacteria was also sterile, but repeatedly grew yeast cells. Bronchoscopy showed nothing of significance. All other tests were also negative.

He received streptomycin 1 gm daily about 50 injections, tetracycline for two weeks and prednisolone for four weeks.

At the Vallabhbai Patel Chest Institute Clinic, four consecutive sputum examinations were negative for acid-fast bacilli by smear and culture and also for bacterial flora. Sputum was also negative for malignant cells repeatedly. Bronchial aspirate was also negative for bacterial flora, acid-fast bacilli and malignant cells.

Bronchoscopy showed nothing of significance. Sputum was positive ten times for Candida albicans by culture and showed heavy growth.

Thymol turbidity test was 20 units/100 ml. Total protein 8.4 gm/100 ml. Tuberculin test was positive for 5 TU. Roentgenologic appearance of the extremities was normal.

Pulmonary tuberculosis, sarcoidosis, bacterial infection and pulmonary malignancy were ruled out.

With the history of diesel fumes which caused his "asthma" like dyspnea, and history of continued consumption of different types of antibiotics along with corticosteroids for a long time aroused suspicion of primary candidiasis of lung, especially when sputum was repeatedly positive and bronchial aspirate was positive for Candida albicans.

When the diagnosis of primary pulmonary candidiasis was made, he was given nystatin aerosol (50,000 units) daily in four divided doses with the help of intermittent positive pressure breathing in inspiration to get wider penetration of the lung. Along with this, nystatin tablets were also given orally 500,000 units four times daily. He began to improve clinically within three days and started getting appetite and sleep at night.

His temperature became normal in about two weeks, and he started gaining weight and the roentgenologic appearance of the lung began to clear. His sputum became negative by culture for C. albicans in three weeks. The patient was allowed to move about in four weeks' time. In about seven weeks, roentgenologically the lungs had cleared completely.

In all, the patient was treated for pulmonary candidiasis for about 11 weeks. Nystatin aerosol was reduced to twice daily after six weeks.

He gained about ten pounds, felt normal and was allowed to resume his usual duties.

DISCUSSION

Diagnosis of bronchopulmonary candidiasis is not easy, especially when Candida albicans is present normally in sputum of some people. Lung biopsy and detection of C. albicans in the lung tissue is the surest method of diagnosis, but this is not practical for day-to-day routine diagnosis. This
is why strict criteria for diagnosis have been followed. In this connection, a warning note is warranted. Chakravarty and Sandhu have shown that after antibiotics, sputum may show heavy growth of C. albicans up to 14 days after antibiotics are stopped. Guarded opinion regarding diagnosis of bronchopulmonary candidiasis should be given during this period before the ecologic balance of the microbiologic flora are restored. The majority of the patients in this series have secondary type of bronchopulmonary candidiasis. Donomae et al found in their study 67.2 per cent secondary candidiasis.

Nystatin is not absorbed in proper concentration in blood when given orally, but two patients in this series with bronchopulmonary candidiasis with heavy growth of C. albicans in sputum, became negative and in two, though sputum did not become negative for C. albicans, there was only scanty growth after therapy with oral nystatin.

It is possible that nystatin is not fully absorbed as nystatin itself, but is broken down into intermediary products which act as antifungal antibiotic. It is probable that nystatin helps in some patients with bronchopulmonary candidiasis in this way even when concentration of nystatin in blood is low. Further study is needed for confirmation.

Aerosol suspension of nystatin in 40 per cent propylene glycol acts well in bronchopulmonary candidiasis. Wider penetration into lung is assured when given through intermittent positive pressure breathing in inspiration. This is a good method, as it can act directly in lungs and can work sufficiently in high concentration against C. albicans. It is noted that nystatin, when given in higher concentration for a longer time, causes irritation of bronchi by nystatin particles and irritating cough may be produced. One patient in this series had irritating cough after administration of a suspension of nystatin aerosol for more than two weeks. This disappeared when the drug was stopped for two days and then concentration of the suspension was reduced. There is no other side-effect due to nystatin. It should be especially mentioned that there is no record of resistance of C. albicans to nystatin even after long-term treatment.

In this series, the primary pulmonary candidiasis patient had systemic dissemina-

**Figure 1:** X-ray film of the chest taken on October 6, 1965 shows non-homogenous opacity of the right lung.

**Figure 2:** X-ray film of the chest taken on December 30, 1965 shows clearing of non-homogenous opacity after treatment.
tion as evident by the affection of liver function test. Aerosol of nystatin along with oral nystatin have done well in this patient, as after treatment, liver function became normal.

The role of *C. albicans* in causing bronchial asthma has been noted independently by Keeney and Kashkin and associates. According to Kashkin, it is due to the contact of yeast-like fungi in respiratory passages for a long time which play the role of specific allergen. These so-called asthmatic patients had repeated attacks of paroxysmal dyspnea which improved only with energetic nystatin therapy. This has been noted in our series also.

Suspension of nystatin as aerosol combined with oral nystatin may be recommended for bronchopulmonary candidiasis. Of course, when needed, amphotericin B may be substituted.

It is possible that *C. albicans* and some other species of Candida play a role in chronic bronchitis. The exact role is not possible to define as yet. It is suggested that patients with chronic bronchitis who do not improve with conventional treatment be investigated for bronchopulmonary candidiasis.

**SUMMARY**

1. The incidence of secondary bronchopulmonary candidiasis has been reported in 3.7 per cent in chronic bronchopulmonary diseases, but primary bronchopulmonary candidiasis is a rare entity.
2. Eleven patients were found to have bronchopulmonary candidiasis of which one had primary pulmonary disease.
3. Only nine patients received treatment and all improved. It is suggested that patients with chronic bronchitis who do not improve with conventional treatment be investigated for bronchopulmonary candidiasis.
4. Suspension of sterilized nystatin powder (50,000 units) daily in divided doses in 40 per cent propylene glycol in normal saline were given as aerosol.
5. Combination of oral nystatin tablets 2,000,000 units daily in four divided doses with aerosol of suspension of nystatin powder (50,000 units in four divided doses) in 40 per cent propylene glycol in normal saline solution with the help of intermittent positive pressure breathing in inspiration at pressure of 10-15 cm of H$_2$O or with the help of hand nebulizer when positive pressure machine is not available, are recommended. Treatment should be given for at least two to three weeks.

6. One patient with primary pulmonary candidiasis with consolidation of right lung and also of upper portion of left lung improved with the above treatment.

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**RESUMEN**

1. La incidencia de candidiasis broncopulmonar secundaria ha sido reportada en un 3.7% de las afecciones broncopulmonares crónicas, pero la candidiasis broncopulmonar primitiva es una entidad rara.
2. Once pacientes fueron diagnosticados de candidiasis broncopulmonar, en uno de los cuales la enfermedad pulmonar era primaria.
3. Solo 9 de estos pacientes recibieron tratamiento, pero todos mejoraron. Se recomienda que los sujetos afectos de bronquitis crónica que no mejoran con el tratamiento usual, sean investigados en cuanto a la posibilidad de candidiasis broncopulmonar.
4. Hemos empleado unas 50,000 unidades de Nystatin en polvo estéril, suspendidas en glicol-propileno al 40 por ciento en solución salina, administradas en forma de aerosol en varias dosis.
5. Recomendamos asimismo la administración de 2,000,000 de unidades de Nystatin oral diariamente, divididas en cuatro dosis, a más de la suspensión indicada en el párrafo 4, administradas en cuatro dosis mediante el respirador a presión positiva intermitente con presión inspiratoria de 10 a 15 cms de agua o, a falta de este aparato, con un nebulizador de mano.

El tratamiento debe ser continuado por dos o tres semanas por lo menos.

6. Un paciente con candidiasis pulmonar primaria, con consolidación del pulmón derecho y parte superior del izquierdo, mejoró con el tratamiento indicado.

**ZUSAMMENFASSUNG**

1. Über das Vorkommen sekundärer bronchopulmonaler Candidiasis wurde für 3,7% der
BRONCHOPULMONARY CANDIDIASIS

Fälle von chronischer bronchopulmonaler Erkrankung berichtet, jedoch ist eine primäre bronchopulmonale Candidiasis ein seltener Krankheitsbild.

2. Bei 11 Patienten fanden wir eine bronchopulmonale Candidiasis, worunter wir von einem Fall einer primären pulmonalen Erkrankung befand.

3. Es erhielten nur 9 Patienten eine Behandlung, und bei allen trat eine Besserung ein. Es wird vorgeschlagen, daß alle Patienten mit chronischer Bronchitis, die sich bei einer konventionellen Behandlung nicht bessern, hinsichtlich des Auftretens bronchopulmonaler Candidiasis untersucht werden sollten.


5. Eine Kombination oraler Nystatin-Tabletten (2.000.000 Einh.) täglich in 4 gleichen Dosen zusammen mit 40% Propylen-glicol in normaler Kochsalzlösung mit Hilfe der intermittierenden positiven Druckatmung und einem Inspirationsdruck von 10-15 cm HO₂ oder unter Zuhilfenahme eines Handverneblers, wenn ein Gerät zur Erzeugung positiven Drucks nicht zur Verfügung stand werden empfohlen. Die Behandlung sollte wenigstens 2-3 Wochen fortgesetzt werden.


References


For reprints, please write: Dr. Chakravarty, V. P. Chest Institute, University of Delhi, Delhi 7, India.

COMPARATIVE ASSESSMENT OF THROMBOELASTOGRAPHIC AND BIOCHEMICAL INDICES OF COAGULATION

This article deals with an analysis and comparison of biochemical indices with 348 thromboelastograms recorded in 95 patients with disorders of the coronary circulation, in 60 with diabetes mellitus, and in 62 with rheumatism.

The data derived attest to the fact that thromboelastography is a valuable objective method of investigation of blood coagulation activity. However, there is not always a parallelism between thromboelastographic and biochemical changes. In view of this, for the more complete understanding of the process of coagulation and anticoagulation systems of the organism, it is expedient to conduct thromboelastographic and biochemical investigations. The authors consider it most valuable to use thromboelastographic method as a means of control in anticoagulant therapy, since in some instances under the influence of the latter on the thromboelastogram more rapidly there appear signs of hypocoagulation rather than according to data of biochemical investigations.