Original Article

Bacteriological Study, Clinical Appraisals, and Treatment of BCGosis in Thailand

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Background: Bacillus Calmette-Guerin (BCG) vaccine is a live attenuated vaccine derived from a virulent strain of *Mycobacterium bovis*. BCG-related regional lymphadenitis, so-called BCGosis, is one of the common complications following BCG vaccination.

Objective: The purpose of this research was to study the bacteriology of BCGosis focusing on *Mycobacterium bovis*. The clinical presentations, investigations, treatments (both medical and surgical managements), and outcomes of BCGosis treatments were evaluated.

Materials and Methods: A retrospective review was performed of all BCGosis patients less than 1 year old who had failed to respond to medical treatment and had underwent surgical management for fluctuated inflamed BCGosis at the Division of Pediatric Surgery, Siriraj Hospital, from 2006 to 2016. Descriptive statistical analysis was performed.

Results: In total, 36 patients were reviewed. The most common location of BCGosis was the left axilla (58.3%). Almost all patients underwent excision, but there was only one patient underwent incision and drainage. AFB stains from the pathologic specimens and bacteriologic study were positive in 33.3% and 16.7% of cases, respectively. *Mycobacterium bovis* was isolated from the culture of 13 patients (36.1%). The conventional PCR test for *Mycobacterium tuberculosis complex* was performed in 33 patients, with a positive finding in only 24.2% of cases. No patients had surgical complications. Anti-tuberculosis drugs were given to 22 patients following the operation. The one-year recurrence-free time in this study was 93.8%.

Conclusion: Investigations for making a diagnosis of BCGosis have significant limitations. Further extensive investigations are needed for identification of the *Mycobacterium bovis (BCG)* stain from other strains of *Mycobacterium tuberculosis complex*. Surgical excision is the mainstay of treatment for BCGosis with a fluctuated inflamed mass with a low recurrence rate. The role of anti-tuberculosis drugs is still unclear, but the author believes they have benefits in cases with a positive *Mycobacterium bovis* culture.

Keywords: BCG, Mycobacteria, Tuberculosis

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Bacillus Calmette Guerin (BCG) vaccine is recommended for routine use in babies soon after birth in countries with a high tuberculosis prevalence, including Thailand. It has been used in The Expanded Programme on Immunization (EPI) since 1977. BCG vaccine is a live attenuated vaccine derived from a virulent strain of *Mycobacterium bovis*. Although it has benefit as a vaccine against *Mycobacterium tuberculosis* and is considered to be safe, it can cause disease in humans, especially in those with impaired immunity, such as severe combined immunodeficiency disease (SCID), chronic granulomatous disease (CGD), or human immunodeficiency virus (HIV) infection[1]. BCG-related regional lymphadenitis, so-called BCGosis, is one of the common complications following BCG vaccination in children[2] (Figure 1).

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These following features lead to the suspicion of BCG as the etiology of lymph node enlargement[3]:

1) History of BCG vaccination on the ipsilateral arm.

2) Onset is usually 2 to 4 months after BCG vaccination. Although it may range from 2 weeks to 6 months, almost all cases occur within 1 year.

3) There is an absence of fever or other constitutional symptoms.

4) Absent or minimal local tenderness over the lesion.

5) Only 1 to 2 discrete lymph nodes are enlarged (clinically palpable) in the majority of cases.

It is difficult to differentiate the *Mycobacterium bovis (BCG)* strain from *Mycobacterium tuberculosis complex*, which comprises *Mycobacterium tuberculosis*, *Mycobacterium africanum*, and *Mycobacterium microti*. However, differentiation of the *Mycobacterium bovis (BCG)* strain from *Mycobacterium tuberculosis complex* is important in order to optimize medical treatment. In cases of simple BCGosis, observation or minimal medical treatment, such as isoniazid, is appropriate[4]. However, in complicated cases

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that fail to respond to medical treatment, such as fluctuated inflamed BCGosis or the progressive spreading of BCGosis even when receiving isoniazid treatment, surgical excision is the best solution. This treatment protocol is totally different from that for *Mycobacterium tuberculosis complex*, in which surgery is reserved for tissue and laboratory diagnosis and the mainstay of treatment would be protocols involving a combination of many anti-tuberculosis drugs. Unfortunately, few publications and case reports studying BCGosis in detail have been published.

The purpose of this research was to study the bacteriology of BCGosis, focusing on *Mycobacterium bovis*. The clinical presentations, investigations, treatments (both medical and surgical management), and outcomes of BCGosis treatments were evaluated and are discussed herein.

Materials and Methods

The present study was approved by Siriraj Institutional Review Board, COA. No. Si 357/2017. A retrospective review was performed of the medical records of all BCGosis patients less than 1 year of age who had failed to respond to medical treatment and had underwent surgical management for fluctuated inflamed BCGosis at the Division of Pediatric Surgery, Siriraj Hospital, between January 2006 and December 2016.

The exclusion criteria were: 1) known case of tuberculosis, 2) primary or secondary immunodeficiency syndrome, 3) no history of BCG vaccination or an obvious BCG scar, 4) had previously undergone an operation on the shoulder, arm, axilla, or chest wall.

Data including the patients' basic demographic data, clinical characteristics, bacteriological investigations, types of treatment, complications, and outcomes of treatment for BCGosis were collected. All the data were processed through the SPSS Statistics program and descriptive statistics analysis was carried out. The present study was approved by the Siriraj Institutational Review Board (340/2560(EC3)).

Results

Although, there were many BCGosis patients treated at Siriraj Hospital in the study period, this study only included patients who had failed to respond to medical treatment and had underwent surgical management for fluctuated inflamed BCGosis. The reason only surgical cases were included was that we wished to study the bacteriology of BCGosis focusing on *Mycobacterium bovis*.

In total, 38 BCGosis patients were identified who had been surgically treated in this study population. Of these, 2 patients with DiGeorge syndrome were excluded due to primary immunodeficiency syndrome. The records of the remaining 36 patients were reviewed, comprising 21 male (58.3%) and 15 female (41.7%) patients. The age of the patients at presentation was between 1 and 8 months and the median age at presentation was 2 months old (Figure 2).

Clinical presentations

The most common location of BCG vaccination was the left shoulder (91.7% of cases). Other locations composed of 2 left buttocks and 1 right shoulder (Figure 3). As stated above, this study population comprised BCGosis patients who had failed to respond to medical treatment. In patients who had received BCG vaccination at the left shoulder, the sites of BCGosis were the left axilla lymph nodes (66.7%), left supraclavicular lymph nodes (27.3%),

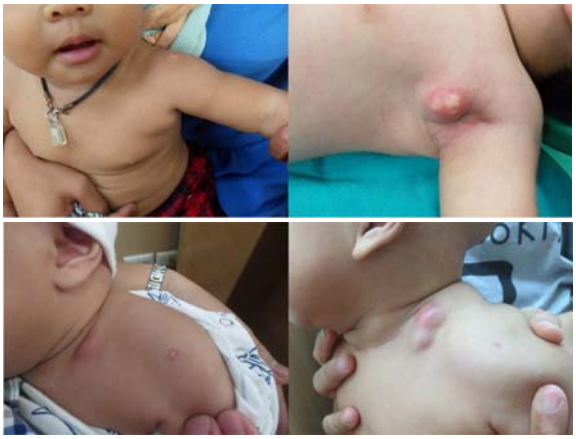

Figure 1. Infants with BCGosis showing an enlargement of the lymph nodes at the ipsilateral side of the BCG scar.

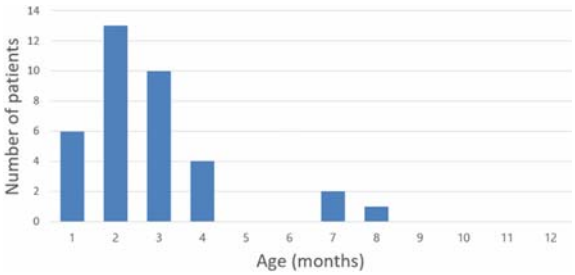

Figure 2. Age of patients at presentation.

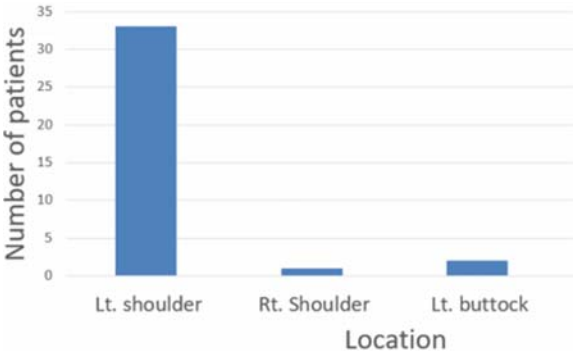

Figure 3. Location of BCG vaccination.

and left cervical lymph nodes (6%), respectively (Figure 4). The median size of the BCGosis was 2 cm.

Treatment

In terms of the previous treatment, 15 patients (41.7%) received antibiotics before the operation, while the same number of patients received no previous drugs, and the remaining 6 patients (16.7%) had a history of receiving anti-tuberculosis drugs (Figure 5 and 6).

Almost all patients underwent surgical excision (97.2%). Only 2.8% of the patients underwent incision and drainage, while no patients received needle aspiration alone. Following operative treatment, 47.2% received both antibiotics and anti-tuberculosis drugs, 36% received anti-tuberculosis alone, and 14% were prescribed antibiotics alone. In patients who received anti-tuberculosis drugs, many drug regimens were prescribed (Figure 7), with the IRZO regimen (Isoniazid, Rifampicin, Pyrazinamide, Ofloxacin) being the most common regimen (36%) in the present study.

Pathological and bacteriological studies

Review of the pathologic examinations revealed non-caseous granulomatous inflammation in 50% of the patients, while 41.6% had caseous granulomatous inflammation. In the other 8.4% of the specimen, pathologists concluded only "Mycobacterium infection".

Acid fast bacilli (AFB) stains from the pathologic and bacteriologic studies were positive in 33.3% and 16.7% of patients, respectively.

Mycobacterial culture for *Mycobacterium bovis* was positive in 36.1% of patients. The polymerase chain reaction (PCR) identification for *Mycobacterium tuberculosis complex* was positive in 24.2 % and negative in 75.8% of patients (Table 1). Also, 19.4% of patients had a positive finding in both the mycobacterial culture for *Mycobacterium bovis* and PCR identification for *Mycobacterium tuberculosis complex*.

Outcomes

No surgical complication was found in this study. The average follow-up period was 7 months. Four patients became lost to follow-up in the first year of treatment.

After the one-year follow-up period, 2 patients presented with recurrent BCGosis. The first case was a male who presented with a BCGosis sized 2 cm at the left supraclavicular lymph node at 2 months of age. Surgical excision was performed at 3 months of age and recurrent BCGosis was noted at 5 months old. The other case was a female who presented with a BCGosis sized 1 cm at the left axilla lymph node at 2 months of age. She underwent surgical excision at 3 months old and recurrent BCGosis was noted

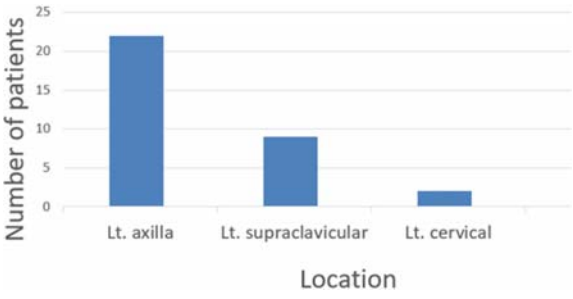

Figure 4. Location of BCGosis in patients who had received a BCG vaccination at the left shoulder.

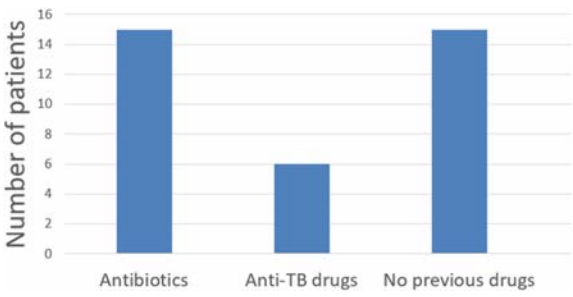

Figure 5. Previous medical treatment before the surgery.

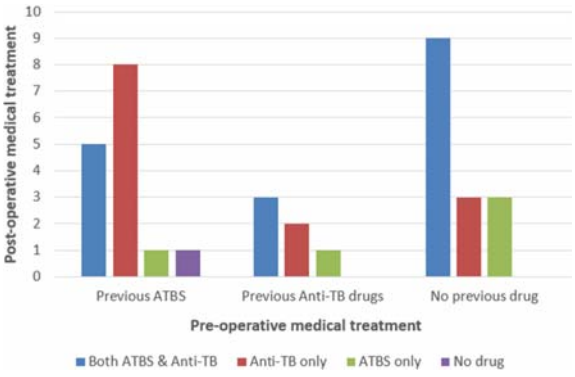

Figure 6. Pre-operative medical treatment in each group.

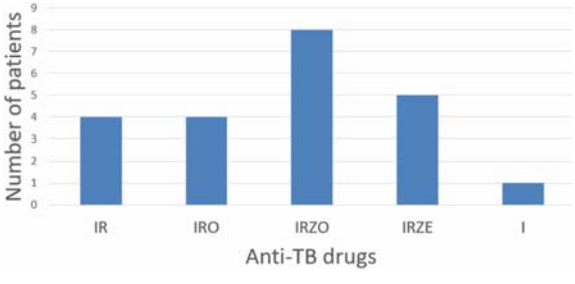

Figure 7. Anti-tuberculosis regimens: I = Isoniazid, R = Rifampicin, Z = Pyrazinamide, E = Ethambutol, O = Ofloxacin.

at 11 months of age. The bacteriological results and treatment are revealed in Table 2A and 2B. Both recurrent BCGosis cases had a positive Mycobacterial culture for *Mycobacterium bovis* and did not receive anti-tuberculosis drugs post-operatively. The recurrence-free rate in this study was 93.8%.

Discussion

Although BCG vaccine has a low incidence of serious adverse reactions, BCGosis or BCG-related regional lymphadenitis can occur in around 1% to 10% of vaccinated individuals[5]. The risk factors associated with BCGosis could be either host related or vaccine related. Host-related factors include age and immunocompetence[3]. Although the neonatal period is associated with a higher risk of BCG-related regional lymphadenitis, the WHO recommendation for BCG vaccination is on the first day of an infant's life. Immuno-compromised hosts have increased complication rates of BCG. In this study, we excluded patients with primary or secondary immunodeficiency syndrome, but on a normal basis, it is not known (before BCG vaccination) whether the neonate might have immunodeficiency syndrome.

The median age at presentation of BCGosis in the present study was 2 months old, which was in line with a previous study, which reported that the onset was usually 2 to 4 months after BCG vaccination. The most common site of BCG vaccination was the left shoulder. Lymph node enlargement almost always develops on the ipsilateral side of the BCG scar, and the left axilla was found to be the most common site of BCGosis in the present study.

The primary objective of this research was to study the bacteriology of BCGosis. Even though the diagnosis of BCGosis was basically clinical presentation, accurate identification of *Mycobacterium bovis* would give important epidemiological and treatment information. The tuberculin skin test is not useful to differentiate reactions caused by *Mycobacterium bovis* from *Mycobacterium tuberculosis*[6]; therefore, laboratory investigations in this study involved pathologic examinations, the acid fast bacilli (AFB) test, mycobacterial culture for *Mycobacterium bovis*, and polymerase chain reaction identification for *Mycobacterium tuberculosis complex*[7].

From our study, almost all pathologic examinations revealed granulomatous inflammation. Non-caseous granulomatous inflammation was found in 50% of the patients and caseous granulomatous inflammation was found in 41.6%. Most of the AFB stains from both the pathologic specimen and bacteriologic study were negative (66.7% and 83.3%, respectively).

Mycobacterial culture for *Mycobacterium bovis* was positive in only 36.1% of specimens. Surprisingly, polymerase chain reaction identification for *Mycobacterium tuberculosis complex* was positive in only 24.2% of patients. Therefore, negative results of mycobacterial culture and PCR identification for *Mycobacterium tuberculosis complex* could

Table 1. Bacteriological results

	Positive	Negative	Not performed
AFB stain (pathologic study)	12 (33.3%)	24 (66.7%)	-
AFB stain (bacteriologic study)	6 (16.7%)	30 (83.3%)	-
Culture (for *M. bovis*)	13 (36.1%)	22 (61.1%)	1 (2.8%) (contaminated)
PCR (for *M. tuberculosis* complex)	8 (24.2%)	25 (75.8%)	3

Table 2A. The first patient with recurrent BCGosis

	BCGosis (first diagnosis)	Recurrent BCGosis
AFB	Pathologic: positive	Pathologic: negative
Mycobact culture	Positive for *M. bovis*	Positive for *M. bovis*
PCR	Negative for MTBC	Negative for MTBC
Previous treatment	ATBS	-
Anti-TB drugs	No	IRZE

Table 2B. The second patient with recurrent BCGosis

	BCGosis (first diagnosis)	Recurrent BCGosis
AFB	Pathologic: positive	Pathologic: negative
Mycobact culture	Positive for *M. bovis*	Positive for *M. bovis*
PCR	Negative for MTBC	Positive for MTBC
Previous treatment	ATBS	-
Anti-TB drugs	No	IRZO

not exclude BCGosis.

The PCR identification test for *Mycobacterium tuberculosis complex* is not specific for *Mycobacterium bovis* and could not differentiate it from *Mycobacterium tuberculosis.* Further investigation, such as using multiplex polymerase chain reaction, phage typing, or microbacterial gene analysis, is required, but these tests are not currently practically applied in routine diagnostic laboratory use[8].

The treatment for BCGosis remains somewhat controversial. BCGosis that has no fluctuated inflamed mass could be treated by many regimens of anti-tuberculosis drugs, although there is no consensus on which anti-tuberculosis regimen is the best one. Some authors have reported that anti-tuberculosis drugs should not be prescribed unless the disease has progressed. However, BCGosis with a fluctuated inflamed mass represents an advanced situation where medical treatment alone will fail. Therefore, a wait-and-see protocol would run the risk of BCGosis turning to a surgical case. Aspiration of a BCGosis with a fluctuated inflamed mass could not be cured and surgical removal would be the best option. Surgical excision is the mainstay treatment for BCGosis with a fluctuated inflamed mass and has a low recurrence rate.

Following surgical excision, the role of postoperative anti-tuberculosis drugs is still unclear. If complete excision has been accomplished, anti-tuberculosis drugs might be stopped. In this series, the cases of two patients with recurrent BCGosis were recorded. Both had positive results of *Mycobacterium bovis* culture and both did not receive any postoperative anti-tuberculosis drugs. Although, the role of postoperative anti-tuberculosis drugs is still unclear, in the author's opinion, a positive *Mycobacterium bovis* culture might have some benefits from the use of anti-tuberculosis drugs postoperatively. No serious surgical complication was found in the present study and the recurrence rate was low.

The present study was limited by its retrospective nature. Several factors, such as vaccine-related factors (dosage of BCG vaccine, residual virulence of the BCG strain, or the quality of the vaccine product) and details of the preoperative antibiotics/anti-tuberculosis drugs usage that might influence the results of the study were not recorded perfectly in the medical records. Moreover, the small number of patients who met the inclusion criteria might not represent the majority of BCGosis cases. More studies in cooperation with pediatric infectious disease specialists are needed to prove the efficacy of anti-tuberculosis drugs so that a guideline for the treatment of BCGosis could be created in the future.

Conclusion

Although clinical features are imperative for making a diagnosis of BCGosis, investigations can help to confirm the diagnosis, although such investigations currently have significant limitations. Further extensive investigations are needed for identification of the *Mycobacterium bovis (BCG)* stain from other strains of *Mycobacterium tuberculosis complex*. Surgical excision is the mainstay of treatment for BCGosis with a fluctuated inflamed mass and has a low recurrence rate. The role of postoperative anti-tuberculosis drugs is still unclear, but the author believes they are of benefit in cases with a positive *Mycobacterium bovis* culture.

What is already known on this topic?

BCGosis is one of the most common complications following BCG vaccination.

Many investigations such as AFB stain, pathological report, mycobacterial culture, PCR for *Mycobacterium tuberculosis* complex may be useful for diagnosis of BCGosis.

Treatments of BCGosis were controversial.

What this study adds?

The clear definition of BCGosis.

Clinical appraisals of BCGosis (common age group, location, size).

Low sensitivity of all investigations for detecting *Mycobacterium bovis* in BCGosis was noted in this study.

AFB stains from pathologic study were positive in 33.3%.

AFB stains from bacteriologic study were positive in 16.7%.

Mycobacterium bovis was isolated from the mycobacterial culture in 36.1%

Positive finding of the conventional PCR test for *Mycobacterium tuberculosis* complex was only 24.2%

Further investigations are required for identification of *Mycobacterium bovis* among other strains of the *Mycobacterium tuberculosis* complex.

Surgical excision is the mainstay of treatment for BCGosis who failed from medical treatments with low recurrence rate.

The role of anti-tuberculosis drugs is still unclear, but in case of positive *Mycobacterium bovis* culture, anti-tuberculosis drugs might have benefits.

Potential conflicts of interest

The authors declare no conflicts of interest.

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การศึกษาทางแบคทีเรียวิทยา อาการแสดง และการรักษาภาวะแทรกซ้อนจากการฉีดวัคซีนบีซีจี

รวิศ เรืองตระกูล, อรพลิน รินทรวิทูรย์

ภูมิหลัง: วัคซีนบีซีจี (Bacillus Calmette-Guerin) เป็นวัคซีนเชื้อเป็นอ่อนฤทธิ์ที่ผลิตโดยใช้เชื้อแบคทีเรีย *Mycobacterium bovis* ภาวะต่อมน้ำเหลืองอักเสบจากบีซีจี (BCGosis) เป็นภาวะแทรกซ้อนอย่างหนึ่งหลังการฉีดวัคซีนบีซีจีที่พบได้บ่อย

วัตถุประสงค์: เพื่อศึกษาทางแบคทีเรียวิทยาของ BCGosis โดยมุ่งเน้นการตรวจพบเชื้อ *Mycobacterium bovis* นอกจากนี้ยังศึกษาเกี่ยวกับอาการแสดง การสืบค้นทางห้องปฏิบัติการต่างๆ การรักษา และผลลัพธ์ของการรักษาของภาวะ BCGosis

วัสดุและวิธีการ: ศึกษาข้อมูลย้อนหลังผู้ป่วยเด็กอายุน้อยกว่า 1 ปี ที่ได้รับการวินิจฉัยว่ามีภาวะ BCGosis ที่ลุกลามเหลวจากการใช้ยารักษาและมีการอักเสบเป็นหนอง ผู้ป่วยรับการรักษาด้วยการผ่าตัดที่สาขากุมารศัลยศาสตร์ ภาควิชาศัลยศาสตร์ โรงพยาบาลศิริราช ตั้งแต่ปี พ.ศ. 2549 ถึง พ.ศ. 2559 โดยวิเคราะห์ข้อมูลด้วยสถิติเชิงบรรยาย

ผลการศึกษา: ผู้ป่วยรวมทั้งสิ้น 36 คนเข้าร่วมในการศึกษานี้ ตำแหน่งที่ต่อมน้ำเหลืองมีการอักเสบบ่อยที่สุดคือรักแร้ข้างซ้าย (58.3%) ผู้ป่วยเกือบทั้งหมด ได้รับการรักษาด้วยการผ่าตัดต่อมน้ำเหลืองออก ผู้ป่วยเพียงรายเดียวที่ได้รับการกรีดระบายหนอง การย้อมเชื้อ Acid fast bacilli (AFB) จากการตรวจทางพยาธิวิทยา และแบคทีเรียวิทยาจากสิ่งส่งตรวจได้ผลบวก 33.3% และ 16.7% ตามลำดับ ตรวจพบ *Mycobacterium bovis* จากการเพาะเชื้อได้ผลบวก 13 ราย (36.1%) ผู้ป่วยจำนวน 33 ราย ได้รับการตรวจปฏิกิริยาลูกโซ่พอลิเมอเรส (PCR) เพื่อตรวจหาเชื้อในกลุ่ม *Mycobacterium tuberculosis complex* และได้ผลตรวจเป็นบวกเพียง 24.2% ไม่มีผู้ป่วยรายใดมีภาวะแทรกซ้อนหลังการผ่าตัดในการศึกษานี้ ผู้ป่วย 22 รายได้รับการรักษาด้วยยาต้านวัณโรคหลังการผ่าตัด เมื่อติดตามการรักษาเป็นระยะเวลา 1 ปี พบว่าผู้ป่วย 93.8% ไม่มีการเกิดเป็นซ้ำของภาวะ BCGosis

สรุป: ปัจจุบันการสืบค้นทางห้องปฏิบัติการเพื่อแยก *Mycobacterium bovis* ออกจาก *Mycobacterium tuberculosis complex* อื่นมีข้อจำกัด การรักษาด้วยการผ่าตัดเป็นการรักษาหลักของ BCGosis ที่มีการอักเสบเป็นหนองโดยพบว่ามีอัตราการเกิดเป็นซ้ำต่ำ บทบาทของการให้ยาต้านวัณโรคยังปรากฏไม่เป็นที่แน่ชัด แต่ผู้วิจัยเชื่อว่ามีประโยชน์ในผู้ป่วยที่ผลการเพาะเชื้อ *Mycobacterium bovis* เป็นบวก