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Original Article

Granulomatous lymphadenitis in Taiwan: Unraveling infantile peak and Bacillus Calmette-Guérin lymphadenitis

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Abstract *Background:* Granulomatous lymphadenitis, a histopathological diagnosis, often indicates infections, such as those caused by mycobacterial and fungal agents.
Methods: We conducted an analysis of 1098 granulomatous lymphadenitis cases, examining age distribution, lymph node locations, and laterality. Molecular detection of Bacillus Calmette-Guérin (BCG) was performed on archived formalin-fixed paraffin-embedded tissue specimens.
Results: Our analysis revealed a bimodal age distribution, notably with a minor peak in infants. These infantile cases predominantly featured axillary involvement, frequently occurring on the left side. Positive rates of BCG identification decreased with age: <1 year, 71%; 1–2 year, 33%; 2–3 year, 13%; 3–4 year, 0%. Remarkably, only one of the 14 cases with molecularly confirmed BCG lymphadenitis had comments regarding BCG in the pathological report. Compared with patients born after 2016 (BCG at 5–8 months), those born before 2016 (BCG at birth) developed BCG lymphadenitis at a wider age range with right skewness (before 2016, 13 ± 11 months [range, 3–33 months] vs. after 2016, 10 ± 2 months [range, 8–13 months]). Four of the 14 BCG-positive cases had congenital heart disease. Seven patients received anti-tuberculosis drugs following surgical excision. No surgical complications were reported.
Conclusions: BCG lymphadenitis constitutes a distinctive minor peak within the spectrum of granulomatous lymphadenitis in Taiwan. Pathologists should consider the possibility of BCG infection, especially in cases of infantile axillary, supraclavicular, neck lymphadenopathies on

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the left side. Moreover, BCG administration at 5—8 months may reduce delayed-onset BCG lymphadenitis.

Introduction

Granuloma is a histopathological finding with various potential causes, including infections, autoimmune disorders, and the presence of foreign bodies.[1—3] Necrotizing granulomas are often indicative of infectious etiologies, particularly mycobacterial and fungal infections.[2—4] When pathologists encounter necrotizing granulomas in lymph node biopsies, they often use special stains like acid-fast and periodic acid-Schiff stains to identify the underlying cause.[3] Common infections leading to granulomatous lymphadenitis include tuberculosis (TB), nontuberculous mycobacteria (NTM) infections, fungal infections, and cat scratch disease.[3,4]

Since special stains can only roughly identify fungus or acid-fast bacilli, without species identification, pathologists frequently incorporate comments in their reports, indicating potential infections and advising additional diagnostic investigations, such as cultures.[3] However, the exact distribution of etiologies in histologically diagnosed granulomatous lymphadenitis has not been clearly explored.

In our retrospective review of granulomatous lymphadenitis cases, we identified a previously unreported bimodal pattern with an infantile minor peak. We present the clinical characteristics of patients in this infantile peak. We hypothesize that these cases represent surgically excised Bacillus Calmette-Guérin (BCG) lymphadenitis cases, which is an etiology rarely mentioned in pathological reports. We confirmed this hypothesis through molecular methods. Additionally, we report the clinical and pathological features of molecularly confirmed BCG lymphadenitis cases.

Methods

Cases

Cases of granulomatous lymphadenitis were selected from the pathological archives. Specimens obtained between 2005 and 2020 were included in this study, and patient age and biopsy site information were extracted from the pathological reports.

BCG identification

Tissue sections cut from formalin-fixed paraffin-embedded (FFPE) tissue blocks were sent to the reference laboratory of the Taiwan Centers for Disease Control for BCG identification.[5] The laboratory employed a patented in-house single-tube triplex real-time polymerase chain reaction (PCR) assay.[6] This assay utilized primers designed to target IS6110, RD4, and a BCG-specific sequence, enabling the identification of *Mycobacterium tuberculosis* complex, the *M. bovis* family, and *M. bovis* BCG, respectively. Signal differentiation was achieved through the use of various fluorescence labels.[6]

Chart review

A comprehensive review of medical records was conducted for BCG-positive cases. This review encompassed age, sex, birth year, underlying diseases, culture results, and the post-operative treatment course.

Pathological review

A meticulous examination of archived slides and pathological reports was performed for BCG-positive cases.

Statistical analysis

Categorical data were compared using the Fisher's exact test, while continuous data were analyzed using the Mann—Whitney test. The Levene's test was employed to assess variances between groups. A p-value of less than 0.05 was considered statistically significant.

Results

Age distribution

Between 2005 and 2020, a total of 1098 cases of granulomatous lymphadenitis were identified from the pathological archives. Fig. 1A illustrates the age distribution, revealing a distinctive pattern characterized by a major peak at the age of 55 and a minor peak in the <1-year age group.

This bimodal pattern prompted us to investigate potential underlying factors. We hypothesized that the minor peak might have a different etiology. Although diseases such as TB, NTM, and cat scratch disease are known to affect children, these conditions do not particularly impact infants aged <1 year, as indicated by existing reports.[7—12] Therefore, these common causes do not explain the observed infantile peak.

Lymph node location

In Fig. 1B, we represented lymph node locations using distinct colors. The most prevalent location was the neck/supraclavicular region, accounting for 60% (655/1098) of cases, followed by the mediastinum at 23% (257/1098). Notably, the axillary region accounted for only 7% (76/1098) of total cases but represented 48% (12/25) of cases within the 0—2 year age range. A significant difference was noted between the 0—2 year age group and other age groups (Fisher's exact test, $p < 0.001$), indicating a remarkable prevalence of axillary lymph node involvement in cases of infantile granulomatous lymphadenitis.

Axillary lymphadenitis may result from infections in the arm, thoracic wall, and breast. Apart from cat scratch

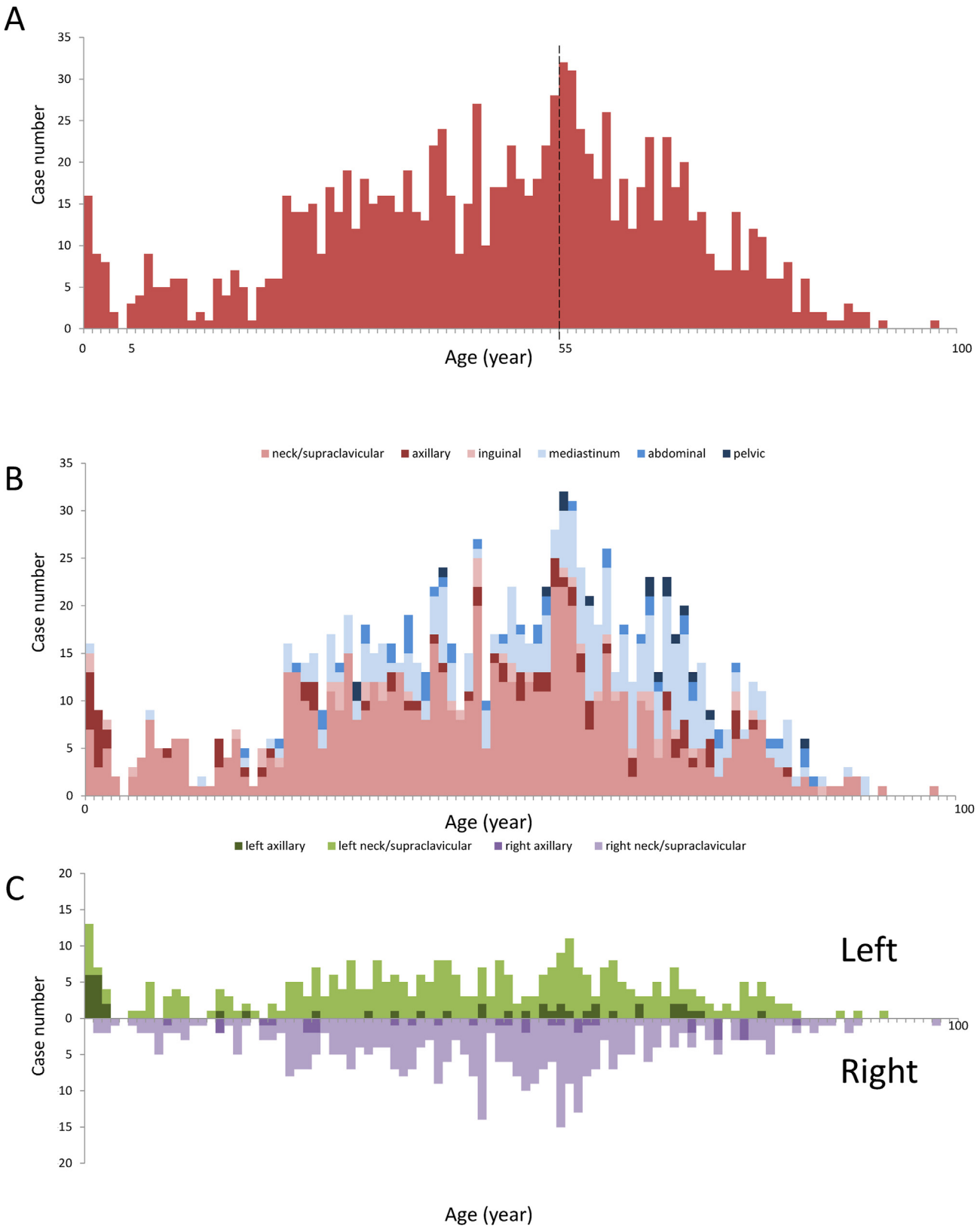

Figure 1. (A) Age distribution of granulomatous lymphadenitis cases. (B) Lymph node location by age. (C) Laterality of neck/supraclavicular and axillary cases by age.

disease, a well-known cause of axillary granulomatous lymphadenitis that frequently affects children,[13] BCG lymphadenitis also commonly manifests in the axillary lymph nodes in infants.[14]

Lymph node laterality

We further analyzed lymph node laterality for neck/supraclavicular and axillary cases, as shown in Fig. 1C. There were a total of 338 left side cases and 365 right side cases, with a balanced distribution of laterality. However, within the 0—2 year age group, a striking observation was made, wherein 91% (20/22) of cases were localized on the left side. This included 12 cases of left axillary and 8 cases of left neck/supraclavicular lymphadenitis. This discrepancy between 0 and 2 years and other age groups was statistically significant (Fisher's exact test, $p < 0.001$).

Considering that BCG vaccination is commonly administered to the left deltoid and is scheduled in newborns to infants, we postulated that granulomatous lymphadenitis cases occurring on the left side of the axillary and neck/supraclavicular regions within the 0—2 year age group could potentially be attributed to BCG lymphadenitis.

BCG identification

To support this hypothesis, we conducted molecular BCG identification on FFPE tissues from patients under five years of age. Out of the 33 patients with adequate residual tissue specimens, 14 tested positive for BCG identification. The results are depicted graphically by age in Fig. 2A. The highest positivity rate was observed in those under 1 year old, with 71% (10/14) testing positive. Positivity rates decreased with age, reaching 33% (3/9) in the 1—2-year-old group and 13% (1/8) in the 2—3-year-old group. There were no positive cases among children older than 3 years. The positive rates differed significantly between age groups (Fisher's exact test, $p = 0.035$).

Furthermore, a comparison between BCG-positive and -negative cases revealed a significant difference in age (BCG-positive, 11 ± 8 months vs. BCG-negative, 21 ± 11 months, Mann—Whitney test, $p = 0.006$; Fig. 2B). With the exception of one case involving a 33-month-old patient, all other BCG-positive cases were under 2 years of age.

Despite the potential for false-negative results associated with FFPE tissue-based PCR tests,[15] our data support to the notion that BCG lymphadenitis constitutes the primary etiology among infantile cases.

Clinicopathological features of BCG lymphadenitis

In Tables 1 and 2, we have provided a list of molecularly confirmed BCG-positive cases. It's important to note that the Taiwanese government shifted the timing of BCG vaccination administration from birth to the 5—8 month age range in 2016.[16,17] In line with this transition, the

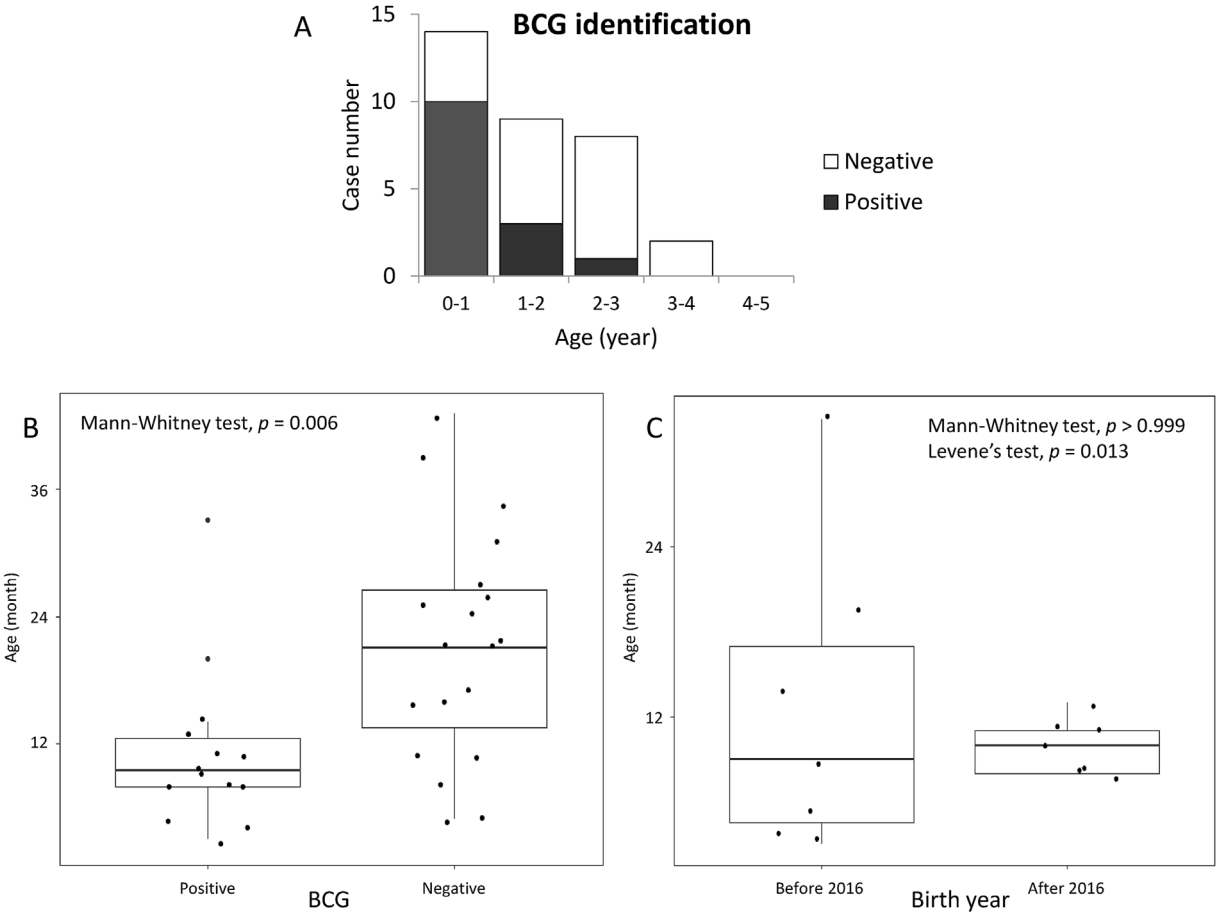

Figure 2. (A) BCG identification results by age. (B) Age of BCG-positive and -negative cases. (C) Age of BCG-positive cases born before 2016 and those in and after 2016.

Table 1 Demographic data and clinical presentation.

No	Age	Sex	Birth after 2016	Underlying diseases	Biopsy site and side	Lymphadenopathy						Fever
						Extent	Duration	Description	Discharge	Fistula	Size (cm)	
1	3 m	F	No	Nil	Mediastinum	Localized	1 m	Not palpable or visible	(−)	(−)	0.5	(+)
2	4 m	F	No	Nil	Axillary, left	Localized	3 m	Soft, non-tender, unmovable mass	(−)	(−)	1.5	(−)
3	5 m	M	No	Nil	Axillary, left	Localized	1 m	Mass with skin erythema	(−)	(−)	1.0	(−)
4	8 m	M	Yes	Nil	Supraclavicular, left	Localized	4 d	Movable mass	(−)	(−)	1.2	(−)
5	8 m	M	Yes	Congenital heart disease (VSD)	Neck, left	Localized	1 w	Elastic mass with skin erythema	(−)	(−)	1.5	(−)
6	8 m	F	Yes	Congenital heart disease (Tetralogy of Fallot)	Axillary, left	Localized	1 w	Elastic mass	(−)	(−)	1.7	(−)
7	9 m	F	No	Nil	Axillary, left	Localized	1 w	Mass with skin erythema	(−)	(−)	3.0	(−)
8	10 m	M	Yes	Nil	Supraclavicular, left	Localized	2 m	No tenderness	whitish	(−)	3.0	(−)
9	11 m	F	Yes	Congenital heart disease (VSD)	Axillary, left	Localized	3 m	Firm movable mass	(−)	(−)	1.0	(−)
10	11 m	F	Yes	Nil	Supraclavicular, left	Localized	3 m	Non-movable mass	(−)	(−)	2.0	(−)
11	1y1m	M	Yes	Primary immunodeficiency	Axillary, left	Localized	1 w	Soft movable mass with skin erythema	(−)	(−)	1.0	(+)
12	1y2m	M	No	Nil	Axillary, left	Localized	5 m	Firm movable mass	(−)	(−)	1.0	(−)
13	1y8m	M	No	Congenital heart disease (DORV)	Neck, right	Bilateral neck	1 m	Non-movable mass	(−)	(−)	2.0	(+)
14	2y9m	M	No	Language delay; hospitalization for 6 times due to various infections	Axillary, left	Localized	10 d	Soft movable mass with skin erythema	(−)	(−)	3.5	(−)

d, day; DORV, double outlet right ventricle; F, female; m, month; M, male; VSD, ventricular septal defect; w, week; y, year.

Table 2 Surgical operation, pathological examination, and postoperative course.

No	Image diagnosis	Operation indication or preoperative diagnosis	Operation method	Other sites involved by granulomas	Pathologist's comment about BCG	Acid-fast stain	Mycobacterial culture	Post-operative medical treatment	Complications
1	CT: a low-density hilar mass encasing right intermediate bronchus	Lung tumor, suspect CCAM	VATS biopsy	Nil	No	Positive	Positive	INH + RIF for 6 months	Nil
2	MRI: suspect hemangioma	Benign soft tissue tumor	Excision	Overlying skin	No	Positive	Negative	INH + RIF for 6 months	Nil
3	Not available	Suspect lymphangioma	Tumor debulking and lymph node dissection	Adjacent soft tissue	No	Negative	Positive	Nil	Nil
4	Not available	Neck mass	Excision	Nil	No	Positive	Not available	INH for 3 months	Nil
5	Not available	Neck mass	Tumor excision and lymph node dissection	Nil	No	Positive	Negative	Nil	Nil
6	Echo: suspect an enlarged lymph node	Axillary tumor	Tumor excision and lymph node dissection	Nil	Yes	Positive	Positive	INH + RIF for 6 months	Nil
7	Not available	Axillary tumor, suspect lymphangioma, infection, or TB	Tumor excision and lymph node dissection	Nil	No	Positive	Negative	INH + RIF for 3 months	Nil
8	Not available	Suspect lymphangioma or BCG infection	Excision	Nil	No	Negative	Negative	INH + RIF for 2 months	Nil
9	Not available	Benign neck mass	Excision	Nil	No	Negative	Negative	Nil	Nil
10	Not available	Suspect TB	Excision	Nil	No	Positive	Positive	Nil	Nil
11	Echo: confluent lymphadenopathy	BCG infection	Excision	Nil	No	Positive	Positive	INH + RIF for 9 months	Nil
12	Echo: An enlarged lymph node	Axillary mass, suspect lymphangioma	Excision	Nil	No	Negative	Not available	Nil	Nil
13	MRI: necrotic lymph nodes, suspected to be an infectious process	Neck mass	Excision	Nil	No	Negative	Negative	Nil	Nil
14	MRI: granulomatous lymphadenitis with caseous necrosis	Axillary mass, suspect TB	Excision	Nil	No	Negative	Negative	Nil	Nil

CCAM, congenital cystic adenomatoid malformation; CT, computed tomography; Echo, ultrasonography; INH + RIF, isoniazid and rifampin; MRI, magnetic resonance imaging; VATS, video-assisted thoracoscopic surgery.

youngest cases (Case 1—3) were all born before 2016, and all of them developed lymphadenitis after receiving the BCG vaccine.

However, we observed a paradoxical distribution of the onset age of BCG lymphadenitis in relation to the change in BCG vaccination administration timing—the oldest cases (Case 12—14) were also born before 2016. The patients born before and after 2016 were compared in Fig. 2C. The average age of patients born before 2016 was 13 ± 11 months (range, 3—33 months; median, 9 months; interquartile range, 14 months), with right skewness (mean > median), whereas the average age of patients born in and after 2016 was 10 ± 2 months (range, 8—13 months; median, 10 months; interquartile range, 3 months). Although the average age showed no significant difference (Mann—Whitney test, $p > 0.999$), patients born after 2016 exhibited a significantly narrower age range than those born before 2016 (Levene's test, $p = 0.013$). This observation suggests that administering the BCG vaccine at 5—8 months old may reduce the incidence of delayed-onset BCG lymphadenitis.

We also attempted to compare the interval from vaccination to lymphadenitis; however, most cases did not have accurate BCG inoculation ages available to calculate this parameter.

Left-sided cases predominated. The only right-sided case (Case 13) presented with bilateral neck lymphadenopathy, which was biopsied on the right side. Apart from this case, all others were unilateral localized, and none displayed disseminated BCG infection.

Among the cases, four patients were diagnosed with congenital heart disease, and Case 11 presented an unspecified primary immunodeficiency. Additionally, the oldest patient, Case 14, experienced recurrent hospitalizations due to various infections. While a definitive diagnosis was not achieved, the possibility of immunodeficiency-related issues cannot be dismissed. It's worth noting that although literature often reports a significant presence of acid-fast bacilli in cases of BCGitis related to primary immunodeficiency,[18] both Case 11 and Case 14 yielded negative results in acid-fast staining.

The pre-operative diagnoses were predominantly tumor or mass. Four of them had pre-operative suspicions of lymphangioma, and one case was suspected of congenital cystic adenomatoid malformation. Among the 14 patients, five had pre-operative suspicions of mycobacterial infection, with two of them specifically suspecting BCG. Regarding pre-operative imaging, only three patients underwent magnetic resonance imaging (MRI), three had ultrasonography, and one had a computed tomography scan. All three ultrasonography diagnoses indicated lymphadenopathy, while two of the three MRI diagnoses were lymphadenopathy with necrosis.

Histologically, all cases showed epithelioid granulomas with necrosis, indicative of typical pathological changes associated with mycobacterial infections.[19] Representative photographs are presented in Fig. 3. The presence of necrotizing granulomas often suggests infection, particularly with mycobacteria (including TB and NTM) and fungi.[20] However, histopathological examination could not specify the exact species.

The pathology report for Case 6 explicitly mentioned the possibility of BCG due to the patient's age and the lymph node's location. In contrast, the pathology reports for the other cases, following routine procedures, merely indicated suspicions of TB, NTM, or fungal infections.

Postoperatively, seven patients received anti-TB drugs. Remarkably, no surgical complications were documented across all patients.

Surgical excision rate of BCG lymphadenitis

In addition, we analyzed our hospital's reported cases to the Taiwan National Surveillance Network of Communicable Disease. From 2011 to 2021, among the 23 cases of BCG lymphadenitis, 16 individuals underwent surgical excision (11 PCR-positive, 5 PCR-negative). The surgical excision rate was 70% (16/23).

Discussion

We identified a distinct age distribution pattern in cases of granulomatous lymphadenitis. Alongside a major peak in middle-aged individuals, we also observed a minor peak in infants. Remarkably, this infantile peak has not been reported in studies from other countries, regardless of whether routine BCG vaccination is practiced or not.[21,22]

We posit that this infantile peak is correlated with BCG vaccination, substantiated by several compelling factors. Firstly, BCG vaccination is routinely administered to infants in Taiwan.[23] Moreover, the locations of left-sided axillary, supraclavicular, and neck lymph nodes align with the typical BCG injection site in the left deltoid. Additionally, PCR testing provides molecular evidence of BCG infection.

Lymphadenitis is a well-known side effect of BCG vaccination, and its occurrence rate can vary depending on the BCG substrain used.[24] The Tokyo-172 strain, used in Taiwan, is associated with a relatively low incidence of side effects.[23,25,26] In fact, the incidence of BCG lymphadenitis in Taiwan is comparable to or even lower than that reported in other countries.[23,27,28]

Therefore, we speculate that the relatively high rate of surgical excisions in Taiwan contributes to the abundance of BCG lymphadenitis pathological specimens. Surgical excision for BCG lymphadenitis remains a debatable treatment, with some studies reporting positive outcomes,[29,30] while others advocate for conservative management.[14,31] Previous research on BCG lymphadenitis in Taiwan has lacked information regarding treatment approaches.

Our calculated surgical excision rate stands at 70%. Consistent with our findings, case series from other regions have reported a significant number of patients undergoing surgical excision, including Singapore (93.5%),[32] South Korea (11.7%),[33] and Thailand (74.7%).[34] While it's possible that cases with mild BCG lymphadenitis symptoms may go unreported, leading to a potential overestimation of the surgical excision rate, our data suggests that an indeterminate proportion of BCG lymphadenitis cases in Taiwan indeed undergo surgical intervention.

In the majority of our cases, the pre-operative diagnosis was primarily tumor or mass, with lymphangioma being the most frequently suspected tumor type. Lymphangioma shares similarities with BCG lymphadenitis in terms of the

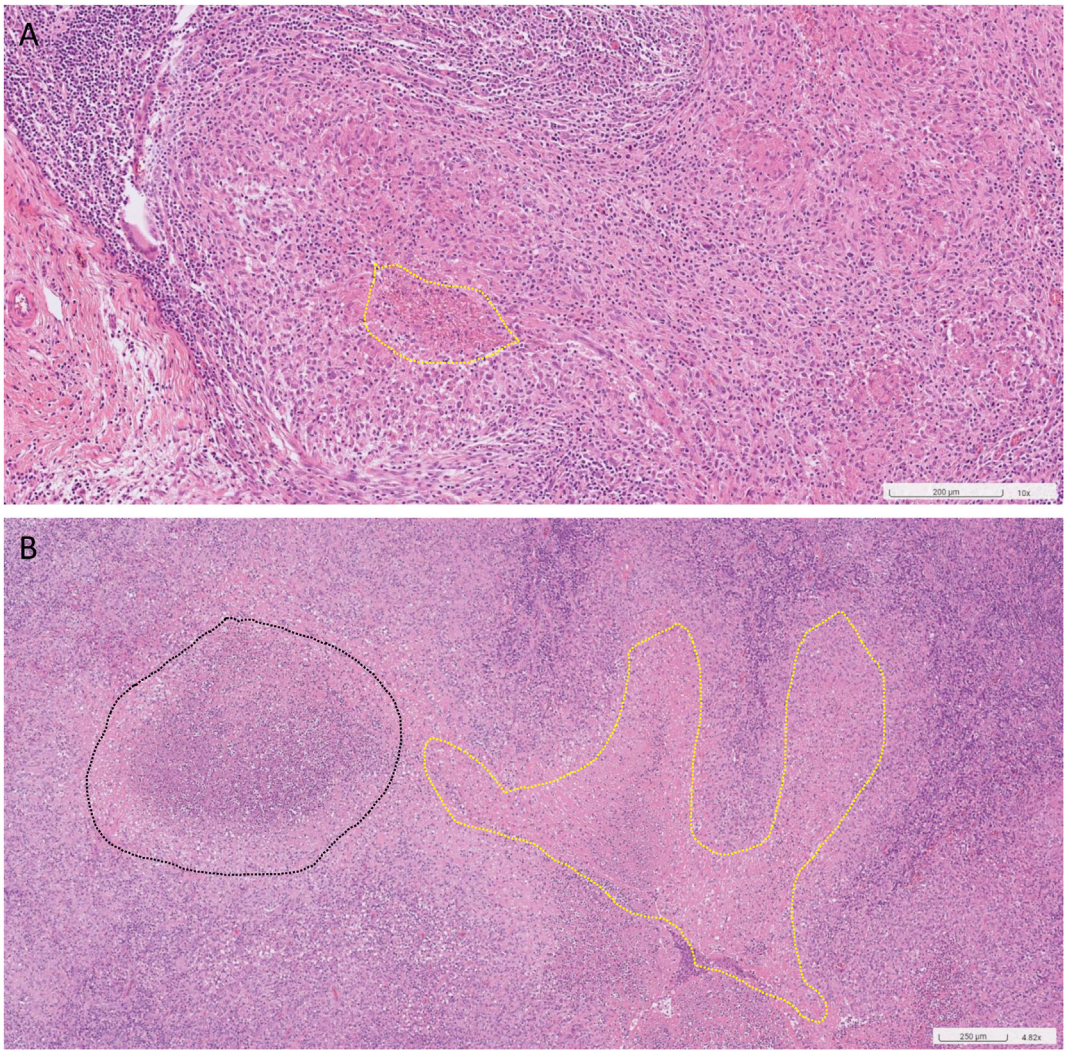

Figure 3. (A) Case 2 showing granulomas with central necrosis (yellow dashed line). (B) Case 6 showing granulomas with serpiginous necrosis (yellow dashed line) and microabscess (black dashed line). These are typical features of mycobacterial infection, but not specific to any species.

age of onset and anatomical site. However, BCG lymphadenitis often manifests additional physical examination findings, such as skin erythema and edema.[14] Furthermore, ultrasonography and MRI can differentiate lymphadenopathy from soft tissue tumors. The integration of physical examination and imaging studies has the potential to improve the precision of pre-operative diagnoses, providing opportunities to explore alternative treatment approaches beyond surgery.

Histopathological research on BCG infection has been extremely limited,[18,35,36] and most studies have lacked molecular evidence of BCG infection.[18,35] Our study, on the other hand, presents a case series of 14 BCG lymphadenitis cases that have been molecularly confirmed, making it the most extensive case series to date with substantial molecular diagnostic evidence.

While previous studies primarily focused on patients with primary immunodeficiency and disseminated BCG infection,[18,35] the majority of our cases presented with localized infection and lacked primary immunodeficiency. This difference in patient profiles may be attributed to variations in patient selection criteria, especially in the context of surgical excision.

In contrast to primary immunodeficiency, congenital heart diseases emerged as the most common underlying condition associated with BCG lymphadenitis in our study. However, more studies are needed to confirm the link between congenital heart diseases and BCG lymphadenitis. It is plausible that children with congenital heart diseases receive more meticulous monitoring for lymphadenopathy, subsequently increasing the likelihood of surgical excision referrals.

Since the age for BCG administration changed in 2016 in Taiwan, comparing cases born before and after 2016 revealed an intriguing result. Cases born before 2016 displayed a broader age range of onset (3—33 months), while cases born after 2016 exhibited a more concentrated age range of onset (8—13 months). These findings suggest that

delaying BCG administration may reduce the incidence of delayed-onset lymphadenitis.

The effects of BCG vaccination administered at 5—8 months old on adverse reactions have been investigated in Japan and Taiwan. A notable decrease in the osteitis/osteomyelitis rate is a major benefit of delayed BCG vaccination.[23,37]

However, the effect on lymphadenitis is still under debate. Following the shift of BCG vaccination to 5—8 month-olds, the incidence increased in Taiwan[23] but did not change in Japan.[37] In addition to changes in incidence, two Taiwanese studies have reported that BCG vaccination at 5—8 months is associated with a shortened interval from vaccination to lymphadenitis.[16,23] A study in Sweden, despite a smaller sample size, comparing BCG administration at birth, 1—5 months old, and 6 months to 6 years old, showed a similar trend in interval change as observed in Taiwan.[38] These observations align with our findings when comparing the ages of BCG lymphadenitis patients.

The mechanism by which delayed BCG vaccination reduces the occurrence of delayed-onset lymphadenitis remains unclear. Here, we aim to put forward some speculative explanations.

Earlier studies have reported varying immune response at different BCG vaccination age. For instance, studies on human immunodeficiency virus-exposed uninfected infants have shown that delaying BCG vaccination by 6—10 weeks leads to a stronger T cell cytokine response.[39] The observation is in line with the dynamic changes in the human immune system from prenatal stages through birth and subsequent maturation.[40,41]

Regarding the pathogenesis of BCG lymphadenitis, we speculate that BCG bacilli are engulfed and initiate intracellular infection within dendritic cells at the inoculation site.[42,43] Subsequently, the bacilli migrate through dendritic cells to draining lymph nodes,[42] where they proliferate, leading to a symptomatic bacterial burden and the development of granulomatous lymphadenitis.

Our hypothetic mechanism of BCG vaccination at 5—8 months old reduces the incidence of delayed-onset lymphadenitis: Infection-susceptible dendritic cells in newborns are fewer compared to those in 5—8-month-old infants because many studies reported a lower number and weaker function of dendritic cells in newborns.[41,44,45] With fewer infected dendritic cells, newborns need a longer time to achieve a symptomatic bacterial burden in the lymph nodes.

To address both lymphadenitis and osteitis/osteomyelitis data, we propose a dual spreading pathways theory (Fig. 4): one involving dendritic cells through lymphatic ducts and the other involving monocytes/macrophages through the bloodstream. In contrast to dendritic cells, the function of monocytes/macrophages is comparable in newborns and adults.[45] Therefore, unlike lymphadenitis induced by dendritic cell lymphatic spread, osteitis/osteomyelitis induced by monocyte/macrophage hematogenous

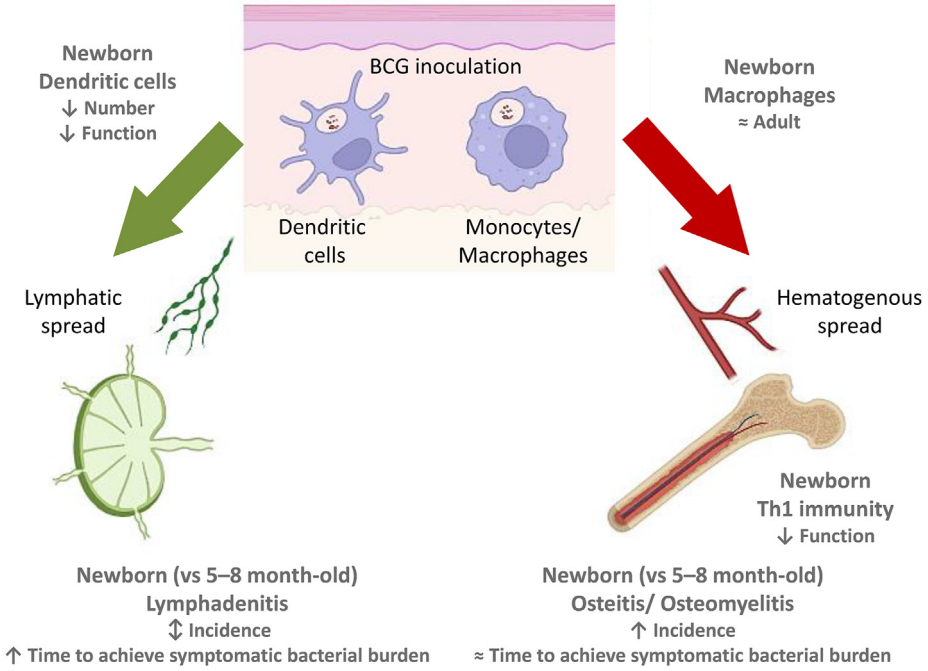

Figure 4. Hypothesis model: Dual pathways of BCG bacilli spreading. BCG bacilli are engulfed by antigen-presenting cells, causing intracellular infection at the inoculation site. Dendritic cells migrate via lymphatic vessels to the lymph nodes, inducing lymphadenitis, while monocytes/macrophages migrate via the bloodstream to the bones, inducing osteitis/osteomyelitis. Newborn dendritic cells are fewer in number and functionally immature, prolonging the time to reach a symptomatic bacterial burden compared to 5—8-month-old infants. In contrast, newborn monocyte/macrophage functionality is comparable to that of adults; thus, the speed of osteitis/osteomyelitis in newborns may not be slower than at 5—8 months old. Newborns might experience a higher osteomyelitis rate due to their weaker Th1 immunity.

spread shows no significant difference in onset time between newborns and 5—8-month-old infants. Additionally, the weaker Th1 immunity in newborns might contribute to an increased incidence.[40,44]

These hypotheses are proposed based on existing literature and our data, attempting to explain clinical observations. However, it's essential to note that these theoretical frameworks regarding the pathogenesis mechanism are largely speculative and require extensive research for validation.

Furthermore, our study has provided the first report on the treatment pattern of BCG lymphadenitis cases in Taiwan. Approximately half of our cases underwent surgical excision as the sole treatment, while the remaining half received a combination of surgical excision and anti-TB drugs. Their treatment approach falls between surgery alone (similar to South Korea)[33] and surgery accompanied by anti-TB drugs (similar to Thailand).[34]

Our data indicates that BCG is one of the most common etiologies of pediatric granulomatous lymphadenitis in Taiwan. However, it appears that many Taiwanese pathologists may not be aware of this condition. We believe that the typical age and biopsy site should raise strong suspicions of BCG lymphadenitis among pathologists, leading them to recommend sending specimens for BCG identification.

One limitation of our study arises from the generally lower DNA quality in FFPE tissues,[46,47] which can potentially lead to false-negative results during PCR-based analyses. In response to this challenge, we conducted molecular testing not only for infantile cases but extended our analysis to encompass all cases under 5 years of age, as the false-negative rate is expected to be consistent across different age groups. Another constraint is that this study is conducted at a single institution, and the surgical excision rate may not necessarily reflect the overall situation in Taiwan. Additionally, our case series exclusively consists of surgically excised cases, potentially introducing bias into the clinicopathological features data.

In conclusion, our study unveils a distinctive age distribution pattern in granulomatous lymphadenitis pathology specimens from Taiwan, characterized by an infantile peak. These cases often correspond to BCG lymphadenitis, primarily affecting the left-sided axillary, supraclavicular, and neck regions—mirroring common BCG vaccination sites. When age and location align, pathologists should consider the possibility of BCG infection, enhancing precision in diagnosis and treatment. Moreover, we observed a reduction in toddler BCG lymphadenitis following the transition from birth to 5—8 months for BCG administration in 2016, implying a decreased occurrence of delayed-onset BCG lymphadenitis.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to language editing and proofreading. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

None.

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