

Clinical Research

Clinical Spectrum of Extrapulmonary Tuberculosis from Pediatric Surgical Perspective

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ABSTRACT

Objective: To identify modes of clinical presentation in extrapulmonary tuberculosis of childhood.

Material and Method: All children diagnosed with extrapulmonary tuberculosis in a pediatric surgery clinic during the years 2000-2017 were reviewed retrospectively. Their files were evaluated for clinical presentation, laboratory and radiologic findings, pathology results, surgical details and postoperative complications.

Results: Six girls and seven boys with the median age of 36 months were evaluated. The most common affected area was axillary lymph nodes in 8 patients and excisional biopsy was performed in all of them. The other foci of tuberculosis were intraabdominal. Abscess emerging from psoas muscle were drained in 2 patients. Ileocecal resection in one and adhesiolysis and biopsy from intestinal wall were performed in the other patient with intestinal involvement. Incisional biopsy was taken in adolescent with ovarian tuberculosis. A congenital immunodeficiency syndrome accompanied in 5 patients and further investigation proved miliary tuberculosis in 2 of them. History of contact with tuberculosis was positive in 4 children. Pathologic examination of surgical specimen showed caseification necrosis in 6 and granulomatous inflammation in all of the cases. Microbiologic evidence for tuberculosis infection was positive in 5 cases. Postoperative complication were adhesive intestinal obstruction in one and skin fistulization in 4 patients. Except the child with miliary tuberculosis and immunodeficiency, all other patients survived the disease with antituberculosis treatment.

Conclusion: Extrapulmonary tuberculosis may be present with various clinical pictures. Surgery has an important role in tissue diagnosis and in complications caused by the disease.

Keywords: Tuberculosis, Extrapulmonary, Child.

ÖZET

Çocuk Cerrahisi Bakış Açısıyla Ekstrapulmoner Tüberkülozun Klinik Spektrumu

Amaç: Çocukluk çağında görülen ekstrapulmoner tüberkülozun klinik başvuru tiplerini tanımlamak.

Gereç ve Yöntem: 2000-2017 yılları arasında bir çocuk cerrahisi kliniğinde ekstrapulmoner tüberküloz tanısı konan tüm olgular geriye dönük olarak değerlendirildi. Dosyalar, başvuru yakınmaları, laboratuvar, görüntüleme, patoloji sonuçları, ameliyat bulguları ve sonrası komplikasyonlar açısından incelendi.

Bulgular: Ortalama yaşı 36 ay olan 6 kız, 7 erkek toplam 13 olgu değerlendirmeye alındı. En sık tutulan bölge 8 olgu ile aksiller lenf nodlarıydı ve tümüne eksizyonel biyopsi yapıldı. Diğer olgularda görülen tüberküloz odakları karın içindedi. Psoas kası absesi olan iki olguda abse drenajı yapıldı. İntestinal tutulumu olan olgulardan birinde ileoçekal rezeksiyon, diğerinde ise adezyolizis ve bağırsak duvarından biyopsi alınması işlemleri yapıldı. Over tüberkülozu olan olgudan ise insizyonel biyopsi alındı. Olguların 5'inde eşlik eden konjenital immün yetmezlik vardı ve bunların 2'sinde miliary tüberküloz tespit edildi. Alınan öyküden, 4 çocukta tüberküloz ile temas olduğu öğrenildi. Patolojik incelemede 6 olguda kazeifikasyon nekrozu ve tüm olgularda granülomatöz inflamasyon tespit edildi. Beş olguda tüberküloz açısından mikrobiyolojik kanıt saptandı. Ameliyat sonrası komplikasyonlar bir olguda adeziv bağırsak tıkanıklığı ve 4 olguda cilde fistül gelişmesiydi. İmmün yetmezlik ve miliary tüberkülozu olan olgu haricinde, tüm olgularda anti-tüberküloz tedavi ile sağkalım elde edildi.

Sonuç: Ekstrapulmoner tüberküloz çeşitli klinik başvuru tablolarıyla karşımıza çıkabilir. Cerrahi girişimler, doku tanısı elde etme ve hastalığın yol açtığı komplikasyonları gidermede önemli rol üstlenir.

Anahtar Sözcükler: Tüberküloz, Ekstrapulmoner, Çocuk.

Bu makale atıfta nasıl kullanılır: User İR, Özokutan BH. Çocuk Cerrahisi Bakış Açısıyla Ekstrapulmoner Tüberkülozun Klinik Spektrumu. Firat Tıp Dergisi 2019; 24 (4): 219-223.

How to cite this article: User IR, Ozokutan BH. Clinical Spectrum of Extrapulmonary Tuberculosis from Pediatric Surgical Perspective. Firat Med J 2019; 24 (4): 219-223.

Tuberculosis (TB) is an ancient infectious disease challenging clinicians from both diagnostic and therapeutic aspects. Although many new techniques have been introduced to identify the bacillus; diagnosis is still based on clinical findings and made empirically in many patients. Anti-TB treatment is long, costly and can cause serious side effects and drug resistance in case of withdrawal. Extrapulmonary TB is a term used to define TB infection in any organ other than pulmo-

nary parenchyma (1, 2). Surgery has two roles in extrapulmonary TB management: one is obtaining specimen for microbiologic, biochemical and pathologic examination and the other is to treat sequelae caused by this infection. In this study, we aim to present our experience with extrapulmonary TB and lessons we learned from pediatric surgical perspective.

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Geliş Tarihi/Received: 24.10.2018

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Kabul Tarihi/Accepted: 10.04.2019

MATERIAL AND METHOD

During January 2000- December 2017, files of patients who were diagnosed extrapulmonary TB in pediatric surgery clinic were reviewed retrospectively. Clinical presentation, laboratory and radiologic findings, surgical details, pathology results, presence of associated pulmonary TB, immunodeficiency, TB-associated morbidity and mortality were noted. This study was approved by local ethics committee for clinical studies (decision number: 2019/81). For data analysis, SPSS statistics programme version 21.0 was used. Mean and median calculations were used for data analysis.

RESULTS

There were 13 children with the median age of 36 months (min: 6 months, max: 192 months) operated with the final diagnosis of extrapulmonary TB. Children younger than 5 years old constitute 53% of the cohort. Gender distribution was even: six girls and seven boys. The most common affected area was axillary lymph nodes in 8 patients. The other foci were abdominal and as follows: psoas muscle in 2, intestinal segments in 2 and ovary in one case. None of the patients had a known history of pulmonary or any other extrapulmonary foci of TB in the preoperative period. Table 1 demonstrates the main clinical characteristics of patients.

Table 1. Clinical characteristics of patients.

Patient	Age (mo)	Gender	Organs-systems effecting TB	Associated immunodeficiency
1	6	M	Intestinal, mastoid bone, pulmonary (miliary TB)	Interleukin 12 receptor beta 1 deficiency
2	18	M	Axillary LAP, pulmonary	Chronic granulomatous disease
3	6	M	Axillary LAP	Chronic granulomatous disease
4	168	F	Ovarian	-
5	192	M	Axillary LAP	-
6	8	F	Axillary LAP	Interleukin 12 receptor beta 1 deficiency
7	144	M	Axillary LAP, pulmonary	-
8	154	F	Psoas muscle	-
9	156	F	Axillary LAP	-
10	36	F	Axillary, mediastinal, abdominal LAP, pulmonary (miliary TB)	Interleukin 12 receptor beta 1 deficiency
11	144	M	Terminal ileum, ascending colon, pulmonary	-
12	18	F	Axillary LAP	-
13	20	M	Psoas muscle	-

Abbreviations: TB: tuberculosis, LAP: lymphadenopathy M: male, F: female, Mo: month.

In patients with TB lymphadenitis, the presenting symptom was swelling in axillary region. Chronic purulent discharge from lymphadenopathy was also observed in 3 of them. Clinical presentation in other children with extrapulmonary involvement were abdominal pain and vomiting in patient 11, acute intestinal obstruction in patient 1, pelvic pain in patient 4 and painless suddenly growing swellings in lateral abdominal wall in patients 8 and 13.

A type of congenital immunodeficiency syndrome accompanied TB in 5 patients and further investigation proved miliary tuberculosis in 2 of them. History of contact with TB in household members was positive in 4 children. Information regarding vaccination status with Bacillus-Calmette-Guerin (BCG) was noted in files of 2 patients (patients 2 and 12) with axillary lymphadenitis and reported as scar associated with vaccine was detected in deltoid region of these patients. Pulmonary involvement was detected in 5 patients after extrapulmonary TB diagnosis was established. C-reactive protein >5mg/l (mean: 51.1±72.2 mg/L) and erythrocyte sedimentation rate >20mm/h (mean: 33.5±37.2 mm/h) were detected in 5 patients. Complete blood count revealed anemia in 8 and lymphopenia in 6

patients. Tumor markers were studied in patient with ovarian TB and CA-125 level was elevated (73 U/ml, normal range: 0-35 U/ml).

In children presenting with lymphadenopathy, ultrasonography (US) was used as the imaging study. Ultrasonography revealed hypervascularity in hilus of lymph nodes in 2 and necrosis in 3 patients. Abdominal X-ray showed air-fluid levels and ascites, thickened intestinal walls and enlarged mesenteric lymph nodes in USG of patient 1 with intestinal involvement. Computed tomography (CT) of chest was performed in postoperative period and showed mediastinal and pulmonary TB. Remaining patients were evaluated with both USG and CT of abdomen. Solid heterogenous mass occupying right ovary in patient 4, abscess emerging from psoas muscle and extending to anterolateral abdominal wall in patients 8 (Figure 1, a&b) and 13 and increased wall thickness of ascending colon and inflamed mesentery in patient 11 (Figure 2) were the detected.

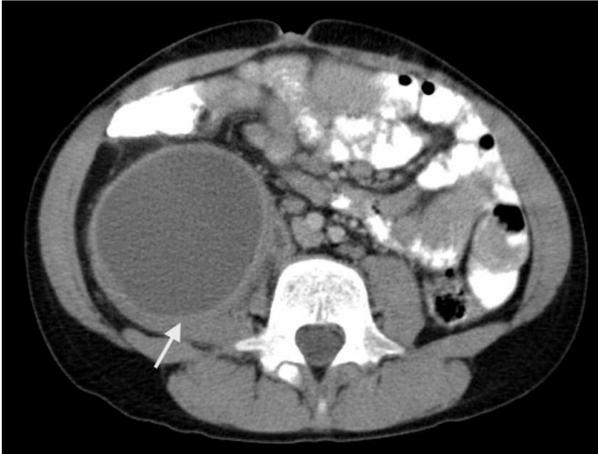


Figure 1a: Abdominal CT image of patient with psoas TB. Arrow points the abscess emerging from psoas muscle.



Figure 1b: Abdominal CT image of patient with psoas abscess extending from retroperitoneum to anterior abdominal wall. Arrow points defect in Spigelian fascia.



Figure 2. Abdominal CT image of patient with intestinal TB. Arrow points the thickened cecal wall.

Surgical procedure was excisional biopsy in patients with lymphatic involvement. Debridement of granulomatous tissue was also performed in children with scrofula formation. Adhesiolysis and biopsies from ileum, peritoneum and mesenteric lymph nodes were performed in patient 1. Incisional biopsy from ovary was done in patient 4. Abscesses were drained and

fascial defects were repaired in patients 8 and 13. Cecum and terminal ileum were excised and the ileum was anastomosed to right colon in patient 11. This decision was made because of suspicion of Burkitt's lymphoma, Crohn's disease and palpation of increased wall thickness of cecum, presence of conglomerated lymphadenopathies in mesentery and need for tissue diagnosis.

Microbiologic evidence of TB was detected in 5 cases (38.4%). Among tissues tested, *Mycobacterium tuberculosis* was cultured in 2/3 cases and polymerase chain reaction (PCR) was positive in 3/8 patients. Ehrlich-Ziehl Neelsen stained acid-resistant bacilli in 4/9 specimens. Table 2 demonstrate microbiologic results of patients. All cases revealed granulomatous inflammation and caseification necrosis in 6 of them.

Table 2. Microbiologic results of patients.

Patient	EZN	PCR	<i>Mycobacterium tuberculosis</i> culture
1	positive	negative	positive
2	negative	not studied	negative
3	positive	not studied	not studied
4	not studied	not studied	not studied
5	negative	negative	not studied
6	negative	positive	not studied
7	not studied	negative	not studied
8	negative	negative	not studied
9	not studied	not studied	not studied
10	positive	positive	not studied
11	negative	negative	not studied
12	positive	positive	positive
13	not studied	not studied	not studied

Abbreviations: PCR: polymerase chain reaction, EZN: Ehrlich-Ziehl Neelsen.

Anti-TB treatment were given according to World Health Organization (WHO) programme in all patients (3). Postoperative complications was intestinal obstruction in adolescent with ovarian TB which resolved with conservative management and fistulization from skin incision in 4 patients; one with psoas abscess and the others with lymphadenopathy. Mortality occurred only in patient 1 with intestinal TB and immunodeficiency in the early postoperative period due to sepsis and multiorgan failure.

DISCUSSION

Today, tuberculosis still affects millions of people and causes mortality. According to WHO, in 2017, 10 million people developed TB worldwide and around twelve thousand new cases in our country (4, 5). Turkey is one of the successful countries in the battle with TB. While the prevalence and mortality caused by the diseases diminished, the treatment success increased over years (6).

Childhood TB differs from adulthood with lower rates of microbiologic proof and higher incidence of developing the disease after primary infection. Before the age of 5, risk of developing hematogenous spread of TB is greater than other age groups. Between 5 and 10 years the risk decreases and rises again during puberty (7).

Our results were in concordance with this data; 7 patients were younger than 5 years old and the remaining patients were older than 12 years old.

Extrapulmonary TB can affect various organs and systems but lymphadenitis is the most common form. Together with meningeal and pleural involvement, they constitute most of the cases (8). Cervical, mediastinal, and axillary lymph nodes are frequently involved sites in all age groups (1). Another study involving only childhood cases of tuberculosis lymphadenitis found that frequency of lymph node regions were similar with adults cases (9). All of our cases had axillary lymphadenopathy. Absence of other sites of lymph nodes can be explained by the fact that pediatricians more frequently refer cervical lymphadenopathy cases to otorhinolaryngology department in our hospital. Although history and physical examination are non-specific, presence of fistulization, hypervascularity in hilar region on Doppler USG can be differentiating from lymphoma or other infectious etiologies (10). BCG vaccine induced lymphadenitis is resistant to medical therapy and usually lead to suppuration, skin fistulization and long healing period with severe scar formation (11). For these reasons and to reduce the time of treatment, abscess drainage or lymph node excision are recommended (12). A recent cochrane systemic review report that the only proven method of treatment for fluctuant/abscessed lymphadenopathy is needle aspiration (13).

Intestinal TB mimics inflammatory bowel disease and presents with similar clinical picture. Definite diagnosis is confirmed by pathologic and microbiologic studies. The study investigating differentiating characteristics of gastrointestinal TB from inflammatory bowel disease found that palpation of abdominal mass, presence of ascites and intestinal obstruction strongly suggest TB. Bowel wall thickening had 70% accuracy for diagnosing TB and 50% for lymphadenopathy regarding abdominal CT findings (14). Presentation and imaging findings of our patients with intestinal TB were in concordance with the literature.

Tubercular psoas abscess usually accompany Pott's disease and rarely colonic TB however can also occur as an isolated focus. Classic treatment of abscess drainage should be employed by either percutaneous or open approach and must be followed by anti-TB medical treatment (15, 16). Both of our patients present with a cold abscess clinic and without vertebral or colonic TB infection. Dramatic clinical improvement achieved after drainage and medical treatment in both cases without recurrence.

Ovarian involvement of TB is important in two aspects: one is the resemblance to malignancy and se-

cond is the risk of future infertility. The most commonly affected age group is young women including adolescents. Abdominal pain and distention as presenting symptom, peritoneal implantations, ascites, septations, heterogeneous mass in radiologic studies and elevated CA-125 level can be seen in both malignancy and TB (17). In this age group, benign tumors predominate and malignancy is rare. For these reasons, before aggressive surgical interventions ending with organ loss, biopsies can be taken by minimally invasive techniques for pathologic and microbiologic examination in patients with diagnostic dilemma. This conservative approach can be beneficial for future fertility and avoid peritoneal adhesions (18). Such conservative approach was preferred in our patient and she received anti-TB therapy in the postoperative period resulting in full recovery. However she experienced intestinal obstruction attacks caused by pelvic adhesions.

Microbiologic proof of TB can not be established in many cases because of two reasons: paucibacillary nature of bacteria and neglecting TB-specific tests on tissues gathered by invasive methods. Microscopic and nucleic acid amplification techniques have been developed but culture remains as the gold standard in diagnosis (19). However it is not an ideal test with significant amount of false negative results. For these reasons, the diagnosis is usually made by a combination of clinical picture, laboratory and imaging studies (1, 19). A study by Gupta et al found that microbiological confirmation could be made in 17% of extrapulmonary tuberculosis patients (14). In another study by Sevgi et al, 65% of patients were started on anti-TB medical treatment without laboratory confirmation based on clinical findings (20). Low rate of microbiologic proof was also the case in our study. Tissues were spared for TB-specific tests in patients with a preoperative suspicion but all tissues were reserved for pathology or aerobic culture in remaining cases. Tuberculosis should still be kept in mind in the differential diagnosis list of lymphadenopathy, abscess or constitutional symptoms of unknown origin.

In conclusion, extrapulmonary TB can present with a wide range of clinical spectrum. The signs and symptoms are nonspecific in most of the cases and can be confused with malignancy or other infectious diseases. Although the mainstay of treatment is medical, surgery plays an important role both in diagnosis by yielding tissue for culture and pathologic examination and treatment of sequel caused by destructive effects of TB infection.

Conflict of Interest: Authors declare that there is no conflict of interest.

REFERENCES

1. Norbis L, Alagna R, Tortolli E, Codecasa LR, Migliori GB, Cirillo DM. Challenges and perspectives in the diagnosis of extrapulmonary tuberculosis. *Expert Rev Anti Infect Ther* 2014; 12: 633-47.
2. Swaminathan S, Ramachandran G. Challenges in childhood tuberculosis. *Clin Pharmacol Ther* 2015; 98: 240-4.
3. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd ed. <http://apps.who.int/medicinedocs/documents/s21535en/s21535en.pdf>. 22.02.2019.
4. World Health Organization. Global Tuberculosis Report 2018. http://www.who.int/tb/publications/global_report/tb18_ExecSum. 22.02.2019.
5. World Health Organization. Tuberculosis profile of Turkey 2018. <https://www.who.int/tb/data/en/>. 22.02.2019.
6. Türkkani MH, Yıldırım Z. Since little time remained to 2015; how far Turkey has achieved to reach the tuberculosis target? *Tuberk Toraks* 2014; 62: 160-4.
7. Carrol ED, Clark JE, Cant AJ. Non-pulmonary tuberculosis. *Ped Res Rev* 2001; 2: 113-9.
8. Kritsaneepaiboon S, Andres MM, Tatco VR, Lim CCQ, Concepcion NDP. Extrapulmonary involvement in pediatric tuberculosis. *Pediatr Radiol* 2017; 47: 1249-59.
9. Neyro SE, Squassi IR, Medín M, Caratozzolo A, Martínez Burkett A, Cerqueiro MC. Peripheral tuberculous lymphadenitis in pediatrics: 16 years of experience in a tertiary care pediatric hospital of Buenos Aires, Argentina. *Arch Argent Pediatr* 2018; 116: 430-6.
10. Gambhir S, Ravina M, Rangan K, et al. Imaging in extrapulmonary tuberculosis. *Int J Infect Dis* 2017; 56: 237-47.
11. Baek SO, Ko HS, Han HH. BCG vaccination-induced suppurative lymphadenitis: four signs to pay attention to. *Int Wound J* 2017; 14: 1385-7.
12. Hengster P, Sölder B, Fille M, Menardi G. Surgical treatment of Bacillus Calmette Guerin lymphadenitis. *World J Surg* 1997; 21: 520-3.
13. Cuello-García CA, Pérez-Gaxiola G, Jiménez Gutiérrez C. Treating BCG-induced disease in children. *Cochrane Database Syst Rev* 2013; 31:CD008300 doi: 10.1002/14651858.
14. Patel B, Yagnik VD. Clinical and laboratory features of intestinal tuberculosis. *Clin Exp Gastroenterol* 2018; 11: 97-103.
15. Aboobakar R, Cheddie S, Singh B. Surgical management of psoas abscess in the Human Immunodeficiency Virus era. *Asian J Surg* 2018; 41: 131-5.
16. Yacoub WN, Sohn HJ, Chan S, et al. Psoas abscess rarely requires surgical intervention. *Am J Surg* 2008; 196: 223-7.
17. Liu Q, Zhang Q, Guan Q, Xu JF, Shi QL. Abdominopelvic tuberculosis mimicking advanced ovarian cancer and pelvic inflammatory disease: a series of 28 female cases. *Arch Gynecol Obstet* 2014; 289: 623-9.
18. Oge T, Ozalp SS, Yalcın OT, et al. Peritoneal tuberculosis mimicking ovarian cancer. *Eur J Obstet Gynecol Reprod Biol* 2012; 162: 105-8.
19. Gupta N, Kashyap B, Dewan P, Hyanki P, Singh NP. Clinical spectrum of pediatric tuberculosis: a microbiological correlation from a tertiary care center. *J Trop Pediatr* 2019; 65: 130-8.
20. Yıldız D, Derin O, Alpay AS, et al. Extrapulmonary tuberculosis: 7 year-experience of a tertiary center in Istanbul. *Eur J Int Med* 2013; 24: 864-7.

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