IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Case Report On Juvenile Idiopathic Arthritis

Karra Geetha[1], Anil Kumar[2], Shaik Razia Begum[2], Nur Hussain[2], T. Rama Rao[3],

1. Associate Professor**,** Department of Pharmaceutics, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, India.
2. Department of Pharm D, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, India.
3. Principal**,** Department of Pharmaceutical Chemistry, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad, India

ABSTRACT: The prevalence of Juvenile idiopathic arthritis (JIA) is 0.86 per 1000 children. Subcutaneous nodules have been reported in 5% to 10% of children with JIA. Approximately 90% of patients with rheumatoid arthritis **(**RA) and subcutaneous nodules test positive for rheumatoid factor (RF), and approximately 40% of all RF-seropositive patients with RA have subcutaneous nodules, whereas only 6% involvement is seen in seronegative cases. We hereby report a case of atypical Juvenile idiopathic arthritis (JIA) in a 6 year old, female child with joint pain & myalgia alongwith subcutaneous nodules over the dorsum of feet, hands and elbows. Joint pain initially involving the left ankle, slowly progressed to involve the knee, shoulder, wrist, metacarpophalangeal and interphalangeal joints over a period of one year. Joint involvement was not symmetric. RF was Negative. Fundoscopy examination was normal. Histopathological examination revealed a central zone of Fibrinoid necrosis surrounded by epithelioid histiocytes and occasional lymphocytes. Differential diagnosis of Rheumatoid Nodule (RN) or Subcutaneous Granuloma Annulare (SGA) or Necrobiosis Lipoidica Diabeticorum(NLD) was made. In light of clinicopathological findings, both SGA and NLD were ruled out and the diagnosis of Juvenile idiopathic arthritis presenting as RF-negative polyarthritis was made.

KEYWORDS: juvenile idiopathic arthritis, rheumatoid arthritis, rheumatoid nodule.

INTRODUCTION:

Juvenile idiopathic arthritis (JIA), previously known as juvenile rheumatoid arthritis encompasses all forms of arthritis that develop before 16 years of age and persist for a minimum of 6 weeks. Rheumatoid nodules (RN) are the most common cutaneous lesion in adult cases of rheumatoid arthritis (RA) and are present in 25% cases (both oligoarticular & polyarticular) [1]. A much greater incidence (75%) is observed in those with RA-associated Felty syndrome.

[2] Approximately 90% of patients with RA and subcutaneous nodules test positive for rheumatoid factor (RF), and approximately 40% of all RF-seropositive patients with RA have subcutaneous nodules, whereas only 6% involvement is seen in seronegative cases. [3] Rheumatoid nodules are clinical predictors of more severe arthritis, seropositivity, joint erosions, and rheumatoid vasculitis. It has been suggested that the presence of RNs often requires more aggressive treatment of the underlying RA to

prevent sequelae. However, in some cases disease progression is independent of nodular disease activity. The prevalence of JIA is 0.86 per 1000 children. Subcutaneous nodules have been reported in 5% to 10% of children with JIA. [4] Rheumatoid nodules are almost always confined to those children with polyarticular arthritis i.e. involving ≥5 joints in first 6 months. [5] Genetics seems to play a role in the appearance of RNs. The HLA-DR4 haplotype (including the heterogeneous group of DRB1 alleles) is predictive of the risk of subcutaneous nodules in RA. [6]

EPIDEMIOLOGY:

Juvenile idiopathic arthritis (JIA) is the most prevalent autoimmune musculoskeletal conditionin children. While the exact incidence of JIA in the U.S. is unclear, estimates suggest it rangesfrom 2 to 20 cases per 100,000 children. In Europe and North America, the prevalence is about 16 to 150 cases per 100,000 children. In North America, oligoarthritis is the most common subtype of JIA, whereas rheumatoid factor-positive (Rf+) polyarthritis is the least common. The condition affects females more frequently than males, with a ratio greater than 2:1, thoughthis ratio varies by subtype[(7)]. The age of onset also varies by subtype: oligoarthritis typically begins at a median age of 4 years, enthesitis-related arthritis (ERA) at 11 years, and Rf+ polyarthritis at 12 years Additionally, ethnicity influences the prevalence of different JIA subtypes, suggesting a genetic component. For instance, African American children are more likely to develop polyarticular and Rf+ forms of the disease, while oligoarthritis is more common among White children of European descent, and enthesitis-related arthritis is more prevalent in children of Mexican and Asian backgrounds [(8)].

PATHOPHYSIOLOGY:

The precise cause and development of juvenile idiopathic arthritis (JIA) remain unclear, thoughit is believed that genetic, environmental, and autoimmune factors contribute to the disease. Evidence for a genetic link is supported by the higher concordance rates of 25% to 40% in monozygotic twins and a 15- to 30-fold increased prevalence in siblings compared to the general population .Specific genes, such as IL2RA/CD25 and VTCN1, have been implicated in increasing susceptibility to JIA. For patients with enthesitis-related arthritis (ERA), the presence of the human leukocyte antigen (HLA)-B27 is common and has been associated withinflammation of the axial skeleton, particularly the hip.[(8

Certain environmental factors are thought to have a protective effect against JIA, including breastfeeding and adequate vitamin D and sun exposure. Conversely, factors such as infections and maternal smoking might elevate the risk of developing or exacerbating the disease[(9)] . More research is needed to fully understand these environmental influences.

The pathogenesis of JIA involves both humoral and cell-mediated immunity. The release of proinflammatory cytokines, like tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-1 due to T-cell activation, is well-documented and a major focus of newer treatments. Radiographic studies have shown increased activation of T cells in the synovium of JIA patients. Diagnostic tests reveal higher levels of TNF-α, IL-6, and IL-1 in polyarticular and systemic JIA (SJIA) compared to other subtypes .Additionally, the activation of the humoral immune response is evident from the presence of autoantibodies such as antinuclear antibodies (ANA) and increased levels of serum immunoglobulins, including IgM rheumatoid factor. ANAs are found in 30% to 50% of JIA patients and are associated with a higher risk of uveitis,a common complication of the disease.

Juvenile Idiopathic Arthritis (JIA) involves both humoral and cell-mediated immune responses in its

pathogenesis. The cell-mediated immune system plays a central role, with the activationof T-cells leading to the release of proinflammatory cytokines such as tumor necrosis factor- alpha (TNF-α), interleukin (IL)-6, and IL-1. These cytokines are well-established in the pathogenesis of JIA and have become the target for many newer medications. Studies,including radiographic models, show an increased presence of activated T-cells in the synovium of JIA patients. Diagnostic testing further supports these findings, revealing that patients with polyarticular and systemic JIA (SJIA) exhibit higher levels of TNF-α, IL-6, and IL-1 compared to other JIA subtypes .

In addition to the cell-mediated response, the humoral immune system is also activated, as evidenced by the production of autoantibodies like antinuclear antibodies (ANA), complement activation, and elevated serum immunoglobulins (Igs) such as IgM rheumatoid factor. ANAs are detected in approximately 30% to 50% of JIA patients and are strongly associated with thedevelopment of uveitis, a common complication of JIA.[10]

distinct JIA subtypes based on joint involvement patterns, serologic markers, and systemic manifestations observed within the first 6 months of illness (Petty et al., 2004). The ILAR subtypes include systemic, oligoarticular, polyarticular, enthesitis-related, psoriatic, and undifferentiated arthritis. Diagnosing JIA typically relies on identifying clinical symptoms andserologic markers specific to each subtype. Accurate classification is crucial as it guides prognosis, potential outcomes, and the selection of appropriate treatment approaches.[11]

Nonpharmacologic Treatment:

Managing juvenile idiopathic arthritis (JIA) requires a multidisciplinary approach. Treatment includes both nonpharmacologic and pharmacologic strategies. Nonpharmacologic therapies, such as physical, occupational, and psychosocial interventions (including mental health and psychiatric support), play a crucial role in managing the condition alongside medications.[12] Techniques like using assistive devices (e.g., wheelchairs and walkers), aerobic conditioning, and splinting help preserve physical function and prevent disability. Psychiatric counseling is also beneficial, as many children with JIA experience anxiety and depression due to chronic pain and the impact on their ability to engage in typical childhood activities.

Pharmacologic therapy should be started with the involvement of the child to ensure they understand their treatment and adhere to it. It's important for healthcare providers and parentsto collaborate in creating a supportive environment that minimizes the child's time away fromschool. In cases where pharmacologic treatments are ineffective, surgical options may be considered**.**

Nonsteroidal anti-inflammatory drugs (NSAIDs) primarily provide relief from pain and stiffness in arthritis but do not address the underlying inflammatory damage caused by the disease. For this reason, NSAIDs are typically used as an adjunctive treatment for patients with moderate to severe Juvenile Idiopathic Arthritis (JIA). Common side effects of NSAID use include abdominal discomfort, gastritis or peptic ulcer disease, and thrombocytopenia. Prolonged use may lead to renal toxicity, such as renal papillary necrosis (Taketomo et al., 2017). To monitor for potential adverse effects, a complete blood count (CBC), liver function tests (LFTs), and serum creatinine levels should be assessed before starting NSAIDs and at least twice yearly for those using them daily, and once yearly for routine use.[13]

Pharmacological Treatment:

The pharmacological treatment of juvenile idiopathic arthritis (JIA) aims to control inflammation, reduce pain, prevent joint damage, and improve quality of life. Treatment strategies are tailored based on the type of JIA, disease severity, and individual patient characteristics. The treatment approach typically progresses in a stepwise fashion, beginning with less aggressive therapies and escalating as necessary. Here's an overview of the main pharmacological treatments used:

1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Use: NSAIDs are often the first-line treatment, particularly for patients with mild disease orsystemic symptoms.

Examples: Ibuprofen, naproxen, and indomethacin.

Mechanism: NSAIDs reduce inflammation and provide pain relief by inhibiting cyclooxygenase (COX) enzymes.

Limitations: NSAIDs do not modify the disease course and are generally used for symptomaticrelief in less severe cases.

2. Glucocorticoids

Use: Intra-articular glucocorticoid injections (such as triamcinolone hexacetonide) are used for localized joint inflammation, especially when fewer joints are affected. Systemic glucocorticoids may be used in severe cases, particularly in systemic JIA or during disease flares.

Administration: Injections are typically given directly into the joint, while oral or intravenous glucocorticoids are used for systemic disease.

Effectiveness: These can quickly reduce inflammation and provide relief, but long-term use isavoided due to side effects like growth suppression and osteoporosis.

Examples: Triamcinolone hexacetonide (TH) and triamcinolone acetonide (TA).

3. Disease-Modifying Antirheumatic Drugs (DMARDs)

Conventional DMARDs:

Methotrexate (MTX) is the most commonly used conventional DMARD in JIA and is considered the cornerstone for patients with moderate to severe disease or polyarticular involvement.

Mechanism: Methotrexate reduces inflammation by inhibiting folate metabolism, thereby reducing immune cell activity.

Other DMARDs: Leflunomide, sulfasalazine.

Use: These drugs slow disease progression and reduce joint damage.

Biologic DMARDs:

Biologic therapies are used in patients who do not respond adequately to methotrexate or havemore severe disease activity.

Tumor Necrosis Factor (TNF) Inhibitors:

Examples: Etanercept, adalimumab, infliximab.

Mechanism: TNF inhibitors block the pro-inflammatory cytokine TNF-α, reducinginflammation and joint damage.

Interleukin Inhibitors:

IL-1 Inhibitors (e.g., anakinra) and IL-6 Inhibitors (e.g., tocilizumab) are used in systemic JIA,particularly in patients with fever and systemic features.

Other Biologics:

Abatacept (a T-cell costimulation inhibitor) is used for moderate to severe JIA that doesn'trespond to other treatments.

Rituximab (a B-cell depleting agent) is occasionally used in refractory cases.

4. Janus Kinase (JAK) Inhibitors Examples:

Tofacitinib.

Use: JAK inhibitors are an emerging class of medications used in patients with more severe orrefractory JIA, targeting intracellular signaling pathways involved in immune activation.

Mechanism: By inhibiting JAK enzymes, these drugs reduce the activity of pro-inflammatorycytokines.

5. Other Therapies:

Corticosteroid-sparing agents: Sometimes other medications, such as hydroxychloroquine orazathioprine, are used to reduce the long-term reliance on glucocorticoids.

Combination therapy: For patients with refractory disease or those who do not respond tomonotherapy, combination treatments involving methotrexate and biologics may be necessary.

6. Treatment Considerations:

Escalation of Therapy: If there is inadequate response to initial therapies (NSAIDs, methotrexate), treatment is escalated to biologic agents or JAK inhibitors.

Regular Monitoring: Patients on long-term DMARD or biologic therapy require regular monitoring for side effects such as infections, liver function abnormalities, or cytopenias.

Tailored Approach: Treatment is individualized based on JIA subtype, disease severity, joint involvement, and patient response.

In summary, the pharmacological management of JIA starts with NSAIDs for mild cases, progressing to DMARDs like methotrexate for moderate disease, and advancing to biologics or JAK inhibitors in more severe or refractory cases. Intra-articular glucocorticoids may be used for localized joint inflammation, with systemic steroids reserved for severe disease flares.

CASE HISTORY:

We hereby report a case of an atypical Juvenile idiopathic arthritis in a 6 year old, female childwith joint pain & myalgia. Joint pain initially involved the left ankle, slowly progressing to involve the knee, shoulder, wrist, metacarpophalangeal and interphalangeal joints over a period of one year. Joint involvement was not symmetric. There was presence of subcutaneous nodules over the dorsum of feet [Figure 1], hands and elbows. Clinical diagnosis of Rheumatoid arthritis was made.

On investigating, rheumatoid factor was negative. Serum ANA and anti-CCP (cyclic citrullinated peptide) antibody tests were advised but not performed. Fundoscopy examination was normal. A skin biopsy was taken from the site of the subcutaneous nodule from the dorsumof the feet. Histopathological examination of the subcutaneous nodule revealed a central zone of fibrinoid necrosis surrounded by epithelioid histiocytes and occasional lymphocytes. [Figures 2 & 3] Differential diagnosis of Rheumatoid Nodule or Subcutaneous Granuloma Annulare (SGA) or Necrobiosis Lipoidica Diabeticorum (NLD) was made.

DISCUSSION:

A diagnosis of rheumatoid nodules is made in the clinical context of the disease. Although biopsies of subcutaneous nodules are occasionally done, they are not useful for diagnosis. [14] The 2010 ACR-EULAR criteria of rheumatoid arthritis has not taken into consideration the presence of rheumatoid nodules or radiographic joint damage because these findings occur rarely in early RA. [15] Many different types of subcutaneous nodules are histologically identical to rheumatoid nodules; mainly NLD and SGA, which are often misdiagnosed as RNs.[16]

In general, RNs tend to be larger and to be confined to the deep dermis or subcutis, at the bony prominences, commonly located at the ulnar aspect of the forearm, elbows, occiput, andlumbosacral area. In our case, the nodules were present on bony prominences of the dorsum of feet and hands. Microscopically they have a central zone of fibrinoid necrosis surrounded by aprominent rim of epithelioid histiocytes and numerous lymphocytes and plasma cells. [1] Fibrin may be deposited in the centre of the granulomas, as opposed to the mucin deposition of SGA.

[17] However, RNs with abundant mucin may be present. [18] Therefore histopathological differentiation between RNs and SGA is difficult.

Serum IgM RF has been found in 75–80% of patients with RA [15]; therefore, a negativeresult does not exclude the presence of this RA in our patient.

Subcutaneous granuloma annulare (SGA) is one of the most common dermatoses with theinvolvement of skin and/or subcutis, usually seen in adults and children, but the aetiology andpathogenesis are unclear. [19] It most often manifests as a large, asymptomatic soft tissue mass. Although nodules are usually stable for months, they may rapidly enlarge over the course of weeks. The typical lesions of SGA are single or multiple, small, pinkish, nonulcerated nodulesin the deep subcutaneous tissue. The most common lesion location is lower extremity, especially the peri-tibial area, followed by the hands. On histological evaluation, these nodules are similar to the nodules seen in adults with rheumatoid arthritis and to the lesion recognizedin adult diabetic patients as necrobiosis lipoidica diabeticorum. [20] Characteristically, the necrobiotic focus is not so large or deeply situated as those of rheumatoid nodules or as broad and diffuse as those of necrobiosis lipoidica (diabeticorum). [16] In our case, one year history of joint pain and migratory polyarthritis along with subcutaneous nodules ruled out SGA and NLD

Necrobiosis Lipoidica is a well-recognized dermatologic complication of diabetes mellitus and may develop in both juvenile (Type I) and adult-onset (Type II) diabetes mellitus. Positive family history of diabetes mellitus has also been one of the risk factors. [13] The sclerodermatous plaque is round to oval, red-brown with an elevated rim. Like SGA, the peri- tibial region is the most common site. Clinical correlation must be taken into consideration before making the diagnosis of NLD. [18] Our patient was not diabetic nor gave any positive family history for diabetes mellitus. The patient was successfully treated with steroids and hasnot shown sustained disease or diabetes mellitus over a one year follow up.

In light of clinicopathological findings, the diagnosis of Juvenile idiopathic arthritis presenting as RF-negative polyarthritis was made. We thus believe that histopathology of rheumatoid nodule presents a special challenge to a pathologist.

Relevant clinicopathological details are essential for diagnosis and appropriate management.

CLINICAL PRESENTATION AND DIAGNOSIS:

The clinical presentation and treatment strategies for juvenile idiopathic arthritis (JIA) vary depending on the specific subtype of the disease. For a diagnosis of JIA to be made, arthritis must persist for at least 6 weeks. Common symptoms include morning stiffness or a "gelling" phenomenon, where stiffness occurs after periods of inactivity, and morning arthralgia that typically improves throughout the day. Various classification systems for JIA have been established by organizations such as the American College of Rheumatology (ACR), EULAR,and ILAR .

The ILAR 2001 classification was introduced to provide a more consistent system compared to the earlier ACR 1977 and EULAR 1978 classifications. This classification identifies six

.

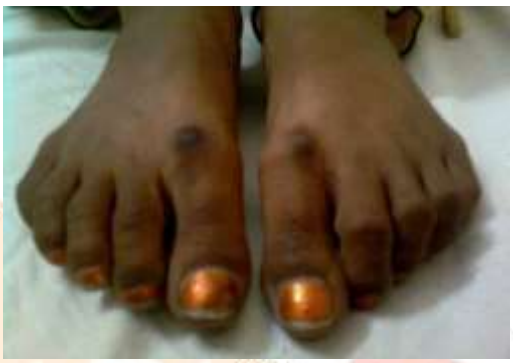

Figure1. Subcutaneous nodules present on the dorsum of foot

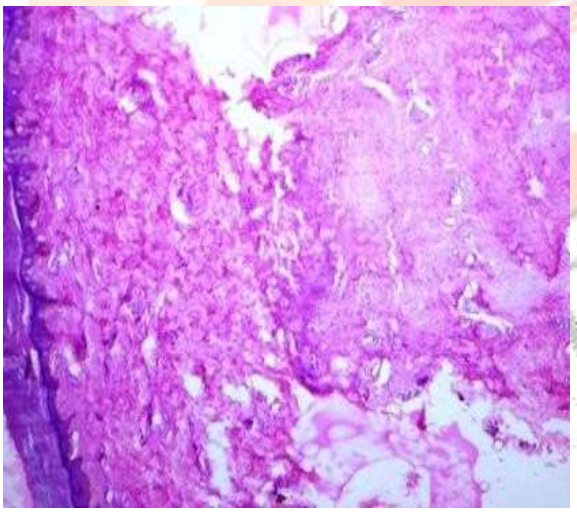

Figure 2. Low power view through subcutaneous nodule showing a necrobiotic focus situated in the deeper dermis. (10x; H&E)

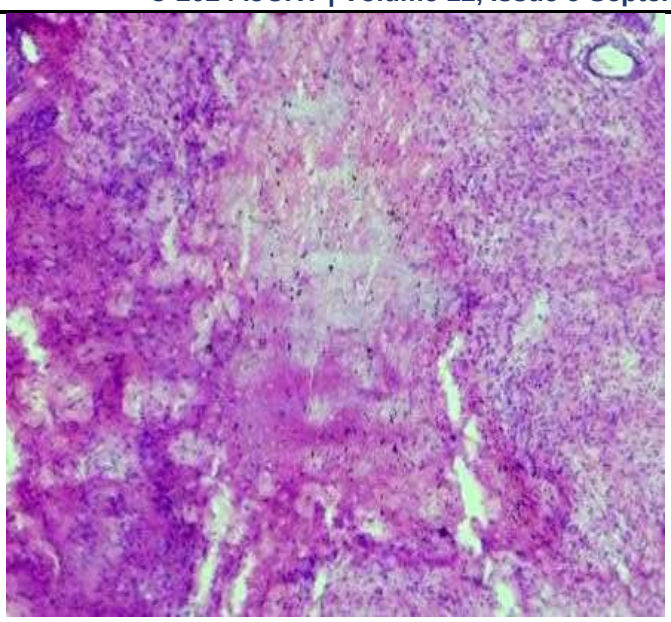

Figure 3. Necrobiotic focus showing central fibrinoid necrosis surrounded by histiocytes and lymphocytes (40x; H&E

REFERENCES:

1. Kumar V, Abbas A K, Fausto N, Aster J C. Robbins & Cotran Pathologic Basis of Disease. 8 th Edition. Philadelphia: Saunders Elsevier; 2010
2. Sayah A, English JC 3rd: Rheumatoid arthritis: A review of the cutaneous manifestations. J Am Acad Dermatol 53:91-209, 2005
3. Kaye BR, Kaye RL, Bobrove A: Rheumatoid nodules. Review of the spectrum of associated conditions and proposal of a new classification, with a report of four seronegative cases. Am J Med 76:279-292, 1984
4. Kaye BR, Kaye RL, Bobrove A: Rheumatoid nodules. Review of the spectrum of associated conditions and proposal of a new classification, with a report of four seronegative cases. Am J Med 76:279-292, 1984
5. Sampath Prahalad and David N Glass. Is juvenile rheumatoid arthritis/juvenile idiopathic arthritis different from rheumatoid arthritis?
6. Ahmed SS, Arnett FC, Smith CA, et al: The HLA-DRB1*0401 allele and the development of methotrexate-induced accelerated rheumatoid nodulosis: A follow-up study of 79 Caucasian patients with rheumatoid arthritis. Medicine 80:271-278, 2001
7. Giancane G, Consolaro A, Lanni S, Davì S, Schiappapietra B, Ravelli A. Juvenile idiopathic arthritis: Diagnosis and treatment. Rheumatol Ther [Internet]. 2016;3(2):187–207.
8. Woo P, Colbert RA. An overview of genetics of paedi- atric rheumatic diseases. Best Practice & Research Clinical Rheumatology. 2009;23:589–97.
9. Ellis JA, Munro JE, Ponsonby AL. Possible envi- ronmental determinants of juvenile idiopathic arthritis. Rheumatology. 2010;49:411–25.
10. Borchers, A. T., Selmi, C., Cheema, G., Keen, C. L., Shoenfeld, Y., & Gershwin, M.

E. (2006). Juvenile idiopathic arthritis. Autoim- munity Reviews, 5, 279-298.

11. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of As- sociations for Rheumatology classification of juvenile idiopathic arthritis: Second revision, Edmonton, 2001. Journal of Rheu- matology. 2001;31:390–2.

12. Ostring GT, Singh-Grewal D. Juvenile idiopathic arthri- tis in the new world of biologics. Journal of Paediatrics and Child Health. 2013;49:E405–12.

13. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, Dewitt EM, et al. AmericanCollege of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis:Initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care & Research. 2011;63:465– 82.

14. Patricia T. Ting and Benjamin Barankin. Dermacase. VOL 5. JANUARY 2005 Canadian Family Physician

15. Longo DL, Fauci AS, Kasper DL et al. Harrison's Principles of Internal Medicine. Volume 2. 18th edition, New York. McGraw Hill Publications. 2012.

16. Hakan Sabuncuoglu et al. Subcutaneous Granuloma Annulare of the Scalp in Childhood: A Case Report and Review of the Literature. Turkish Neurosurgery 2007, Vol: 17, No: 1, 19-22

17. Mills SE, Carter D, Greenson JK et al. Sternberg's Diagnostic surgical pathology. 5 th Edition. Philadelphia. Lippicott Williams & Wilkins. 2010

18. Mckee P H, Calonje E, Granter S R. Pathology of the skin with clinical correlations. Volume 1. 3 rd edition. Philadelphia. Elsevier Mosby. 2005

19. Requena L, Fernandez- Figueras MT. Subcutaneous granuloma annulare. Semin Cutan Med Surg 2007; 26: 96-9

20. Grogg KL, Nascimento AG. Subcutaneous granuloma annulare in childhood:clinicopathologic features in 34 cases. Pediatrics: 107(3):42, 2001