Curr Rheumatol Rep (2013) 15:310
DOI 10.1007/s11926-012-0310-2



# What is the Background Incidence of Malignancy in Children with Rheumatic Disease?

**Melissa L. Mannion · Timothy Beukelman**

Published online: 3 February 2013


**Abstract** Until recently, relatively little was known about the background risk of malignancy in pediatric rheumatic diseases. Worrying reports about the development of malignancies in children treated with new biologic agents have prompted rigorous studies of the incidence of malignancy associated with juvenile idiopathic arthritis (JIA). These studies reveal that JIA is likely to be associated with an increased risk of incident malignancy, irrespective of treatment with new biologic agents. A preliminary study indicates that the background risk of malignancy is also elevated in pediatric-onset systemic lupus erythematosus. On the basis of simple observation, the background risk of malignancy among children with Sjögren syndrome and dermatomyositis seems much lower than the markedly elevated risk found in adults with the same diagnoses. Clearly, the background risk of malignancy must be considered in any evaluation of the safety of new therapeutic agents.

**Keywords** Juvenile idiopathic arthritis (JIA) · Systemic lupus erythematosus (SLE) · Sjögren syndrome · Juvenile dermatomyositis · Malignancy · Pediatrics · Children · Rheumatic disease · Incidence

## Introduction

Pediatric rheumatic diseases, the most common of which is juvenile idiopathic arthritis (JIA) with a prevalence of between 0.07 and 4.01 per 1000 children [1], can directly result in significant pain and other acute and chronic symptoms, as well as long-term disability. Little is known, however, about the adverse effects of the disease on other aspects of health, including potential harmful effects of autoimmunity on immune system function.

Among adults with rheumatoid arthritis (RA), a disease thought to have a similar pathogenesis to JIA, there is good evidence to support the notion that, irrespective of the use of immunosuppressant medications, patients have an increased risk of serious infection [2] and of some forms of malignancy (particularly lymphoma) [3] compared with persons without RA. A recent meta-analysis of cohort studies of adult patients with RA reported a standardized incidence ratio (SIR) of 2.08 (95 % confidence interval (CI) 1.80–2.39) for lymphoma and a SIR of 1.05 (95 % CI 1.01–1.09) for overall malignancy [3]. In addition to RA, other autoimmune rheumatological conditions, for example Sjögren syndrome, systemic lupus erythematosus (SLE), and dermatomyositis have been associated with an increased risk of malignancy in adults.

This increased background risk of malignancy in autoimmune conditions is postulated to result from inflammation, which leads to chronic tissue damage and cellular replication. The malignancy risk is present both systemically and locally in the organ affected by autoimmunity [4]. Autoimmune diseases and malignancy may share risk factors or common etiology. They can have similar cytokine profiles and genetic polymorphisms associated with them, especially those related to apoptosis or gene repair. Patients with RA can have increased DNA damage correlated with disease activity, which can also increase the risk of malignant growth [5]. Because appropriate immune surveillance can eliminate malignant replication, an active immune system is important in the monitoring and regulation of tumor growth. However, excessive proliferation and stimulation of the immune system because of infection, autoimmunity, or inflammation may limit the effectiveness of the immune system in preventing malignant transformation [4].

This article is part of the Topical Collection on *Pediatric Rheumatology*

M. L. Mannion · T. Beukelman (✉)
Department of Pediatrics, Division of Rheumatology,
The University of Alabama at Birmingham,
Children's Park Place 210, 1600 7th Ave South,
Birmingham, AL 35233, USA
e-mail: tbeukelman@peds.uab.edu

M. L. Mannion
e-mail: mmannion@peds.uab.edu

Whether pediatric rheumatic diseases are similarly associated with an increased background risk of malignancy had not been rigorously investigated until recently. This lack of knowledge about the background incidence of malignancy among children with rheumatic diseases, in particular among children with JIA, has complicated attempts to evaluate the safety of new therapeutic agents. More than a decade ago, the advent of tumor necrosis factor alpha inhibitors (TNFi) revolutionized the treatment of JIA and other pediatric inflammatory conditions. These biologic agents proved to be highly effective for the treatment of JIA [1], but enthusiasm for their use was tempered by fears of a possible increased malignancy risk [5]. Based on a report of 48 children who developed malignancy while being treated with TNFi [6], in 2009 the FDA placed a boxed warning about malignancies on all TNFi [7]. Unfortunately, the FDA did not have complete information available to them when the analyses were performed [8, 9]: although the incidence of malignancies (in particular lymphoma) was likely to be higher in children being treated with TNFi than in the general population of healthy children, there were no available estimates of the incidence of malignancy in children with JIA who had never received TNFi therapy. Several investigators have since attempted to determine the background incidence of malignancy among children with JIA using various methodological approaches, data sources, and patient populations.

Clearly, the background incident malignancy risk is a significant concern to patients, families, physicians, and everyone else involved in the care of children with rheumatic disease. Several recent studies have begun to clarify this issue for children with JIA, but there is still little known about the risks associated with other pediatric rheumatic diseases.

## Malignancy in JIA

Concern for a possible increased background risk of malignancy among children with JIA was initially founded primarily upon an increased risk seen in adults with RA. This concern was heightened significantly when voluntary reports of malignancy among children receiving TNFi therapy revealed an increased incidence compared with the general population, leading to a boxed warning by the FDA in 2009. Before the boxed warning, there was only a single published study that attempted to address the incidence of malignancy among children with chronic arthritis.

In 2000, Thomas et al. [10] published the first study evaluating the incidence of malignancy in pediatric patients with inflammatory arthritis. The study used in-patient medical records from Scotland, and compared observed malignancy rates with those reported by the national cancer registry. The study's primary focus was on adult patients with RA and osteoarthritis; however, the sample also included a total of 896 patients (with 6,587 person-years of follow-up) with diagnosis codes for juvenile chronic arthritis. The data are from before the availability of biologic agents; use of other treatments among the study patients is not described. The investigators observed a total of four malignancies; two in male patients and two in females. The types of malignancy were not described. The standardized incidence ratio (SIR) was 1.29 for males (95 % CI 0.14–4.64) and 0.83 for females (95 % CI 0.09–3.01). Despite the point estimates of the SIRs being very close to unity (indicating no increase in the incidence of malignancy), the limited sample sizes produced 95 % confidence intervals showing potential threefold or higher increase in the incidence of malignancy.

Since the FDA boxed warning for TNFi, at least four epidemiological studies of the background incidence of malignancy in JIA have been published. The first of these was a study in 2010 by Simard et al. utilizing several Swedish national Registers [11•]. The investigators identified children with JIA using inpatient and outpatient records and identified five comparator patients for each child with JIA. Follow-up for children with JIA was censored if they received treatment with biologic agents. Overall, the cohorts consisted of 9,020 JIA patients (131,144 person-years) and 44,858 comparator patients (661,758 person-years). Incident malignancies were identified in the national cancer register. Sixty malignancies (11 lymphoproliferative, 10 gastrointestinal, 10 cutaneous, 18 urogenital, three nervous system, three hematological, five other sites) were identified in the biologicals-naïve JIA cohort. In analysis including all ages, all cancers, and all calendar years, there was no significant difference in the relative risk (RR) of malignancy in JIA patients against the comparator group (RR 1.1 (95 % CI 0.9–1.5)). Interestingly, when the data were stratified by calendar year of entry into the JIA cohort, there was a significant difference in the RR; for patients diagnosed with JIA from 1969–1986, the RR was 1.0 (95 % CI 0.7–1.4), and from 1987–2007, it was 2.3 (95 % CI 1.2–4.4). This increased incidence was most pronounced for lymphoproliferative cancers (RR 4.2 (95 % CI 1.7–10.7)). Owing to concern about incomplete knowledge of biologic agent use, the authors performed a sensitivity analysis by truncating follow-up before introduction of biologic agents in 1999, with similar results. One of the major limitations of this study was this inability to study medication use in a detailed fashion. For example, it makes it impossible to ascertain whether the introduction and subsequent widespread use of methotrexate after 1987 contributed to the increase rate of malignancy observed in this more recent cohort of patients.

In 2011, Bernatsky et al. published an evaluation of JIA registries at three Canadian pediatric rheumatology centers, revealing no increased risk of cancer [12•]. Patients were

identified via pediatric rheumatology clinic registries, and incident malignancy cases were identified from provincial cancer registries. Comparator data were derived from expected incidence of malignancy from provincial cancer registries. Their data contained 1,834 JIA patients (22,341 patient-years), and they observed one malignancy during follow-up. The malignancy was Hodgkin lymphoma in a patient with a disease duration of 2.4 years, who had never been exposed to methotrexate or TNFi. The resulting SIR for all malignancies was 0.12 (95 % CI 0.0–0.7), and for hematological malignancies the SIR was 0.76 (95 % CI 0.02–4.21). Patients' individual medication use was not determined in the study, but the authors reported that fewer than 2 % of the JIA patients had been treated with TNFi.

In 2012, Beukelman et al. published a study of the incidence of malignancy in JIA using national United States Medicaid claims data [13•]. Cohorts of pediatric patients with JIA and without JIA (but with a different chronic medical condition, namely attention-deficit hyperactivity disorder (ADHD)) were identified. Detailed medication exposures were determined using pharmacy claims, and observation person-time was divided among three mutually exclusive categories: never exposed to methotrexate or TNFi; ever exposed to methotrexate but never exposed to TNFi; and ever exposed to TNFi irrespective of methotrexate use. Incident malignancies were identified in the medical claims using an identification algorithm followed by a detailed review of all identified cases to determine the likelihood of true incident malignancy (possible, probable, or highly probable). The incidence of probable or highly probable malignancy observed in children without JIA corresponded approximately to the rate expected in the Surveillance, Epidemiology, and End Results (SEER) population based cancer registry. The JIA cohort consisted of 7,812 patients (12,614 person-years) and the ADHD cohort had 321,821 patients (391,984 person-years). A total of seven probable or highly probable incident malignancies were identified in the JIA cohort (two leukemia, three brain, and two other solid malignancies). Using the age, sex, and race standardized malignancy rate in the ADHD cohort as an internal comparator, the SIR for malignancies within the entire JIA cohort was 4.4 (95 % CI 1.8–9.0), and the estimate varied based on medication exposure. The SIR associated with no use of methotrexate or TNFi was 6.9 (95 % CI 2.3–16); that for ever methotrexate use without TNFi was 3.9 (95 % CI 0.4–14), and that for any TNFi use was 0 (0–9.7).

Also in 2012 Nordstrom et al. published analyses of data from the PharMetrics Patient-Centric Database, which contains medical and pharmacy claims from the United States [14]. The investigators identified a cohort of JIA patients that had not been exposed to TNFi or other biologic agents (3,605 subjects and 5,974 patient-years of follow-up) and matched non-JIA patients (37,689 subjects and 73,395 patient-years of follow-up). They identified four cases of malignancy (two lymphoma and two solid cancer) in the JIA cohort. The incidence of malignancy was higher in the children with JIA than in the children without JIA (hazard ratio (HR) 2.8 (0.98.3)). The incidence of malignancy in children with JIA was also significantly elevated compared with SEER incidence rates (SIR 4.0 (95 % CI 2.6–6.0)).

The salient results of each of these studies are summarized in Table 1. The heterogeneity of study design, JIA patient population, and choice of comparators in the studies does not enable simple meta-analysis. Nevertheless, taken together these epidemiological studies suggest that children diagnosed with JIA are more likely to develop cancer than the general population. The three recent studies, with the largest number of children with JIA, all resulted in a two to fourfold increase in malignancy risk. It is unclear why the Canadian study by Bernatsky et al. alone showed no increased risk of malignancy associated with JIA. This study utilized records maintained at individual pediatric rheumatology centers to identify children with JIA, whereas the other three recent studies utilized data generated from billing records or registers to identify children with JIA. It is uncertain whether this difference could in part account for the discrepant results.

Among adults with RA, a correlation between higher disease activity and increased cancer risk (irrespective of treatment received) has been demonstrated [15]. Whether or not a similar association is present among children with JIA has not been reported. If such a relationship does exist, it may be that newer biologic agents, for example TNFi, may in fact help counter this increased background malignancy risk via improved control of the autoimmune process. Irrespective of this possibility, it is clear that safety evaluation of new therapeutic agents for JIA must include adequate comparator groups of children with JIA who did not receive the agent being studied if it is to produce interpretable results. Adequate comparator data for these analyses would probably be best obtained through the recently proposed institution of a disease-wide serious adverse event registry [16].

## Malignancy in Pediatric Systemic Lupus Erythematosus

SLE has been associated with an observed increased risk of malignancy among adults. In several adult cohort studies from various geographical locations (Taiwan, California, and an international cohort including Canada, United States, United Kingdom, Iceland, Sweden, Korea) the SIR for all malignancies revealed a modest but statistically significant elevation of approximately 1.15. The SIR for Hodgkin lymphoma was generally higher, in the range of a threefold increase, and the SIR for non-Hodgkin lymphomas were higher still [17–20].

**Table 1** Published rate ratios for the incidence of malignancy among children with JIA

| Study author and year | Number of JIA patients | Patient-years of follow-up | Rate ratio (95 % CI) |
|---|---|---|---|
| Thomas, et al 2000 [10] | 896 | 6,587 | SIR 0.8 (0.09–3.0) (female) |
| | | | SIR 1.3 (0.1–4.6) (male) |
| Simard, et al 2010 [11•] | 5,296 | ~25,000 | RR 2.3 (1.2–4.4) |
| Bernatsky, et al 2011 [12•] | 1,834 | 22,341 | SIR 0.12 (0.0–0.7) |
| Beukelman, et al 2012 [13•] | 7,812 | 12,614 | SIR 4.4 (1.8–9.0) |
| Nordstrom, et al 2012 [14] | 3,605 | 5,974 | HR 2.8 (0.9–8.3) |

*JIA* juvenile idiopathic arthritis; *CI* confidence interval; *SIR* standardized incidence ratio; *RR* relative risk; *HR* hazard ratio

There have not yet been any published epidemiological studies on the incidence of malignancy in pediatric SLE patients. Results from a preliminary study presented by Bernatsky et al. identified 797 children with SLE who were treated at seven North American pediatric rheumatology centers [21]. Regional tumor registries were then searched for these patients with SLE. Medication usage was not taken into account in the analyses. Overall, nine malignancies were identified, with a resulting SIR of 4.3 (2.0–8.1). The incidence of hematological malignancies was also increased (SIR 6.7 (1.4–19.5)). These preliminary data suggest an increased malignancy risk associated with pediatric-onset SLE that may be similar to that seen in the adult population. As with JIA, it will be important to consider the background malignancy risk associated with pediatric-onset SLE when evaluating the safety of medications. If the background malignancy risk can be modified by improved disease control, this should also be considered in evaluating the potential benefits of effective therapy and the risks of inadequate disease control.

## Malignancy in Pediatric Sjögren Syndrome

There is a strong association between Sjögren syndrome and lymphoma in adults. Kassan et al. first described an association between adults with Sjögren syndrome and lymphoma in 1978; women with Sjögren syndrome had a 44-fold increased risk of non-Hodgkins lymphoma compared with the general population [22]. In another more recent cohort study of adult Sjögren syndrome patients, the SIR for all malignancies was 1.42 (95 % CI 0.98–2.00) and for non-Hodgkin lymphoma the SIR was 15.57 (95 % CI 7.77–27.85) [23].

The incidence of malignancy in pediatric Sjögren syndrome patients has not been published. In particular, to our knowledge there have been no published cases of lymphoma or other malignancy developing in a child diagnosed with Sjögren syndrome [24]. The reasons for this are unclear, but it may be a result of a latency period in the subsequent development of lymphoma that delays the clinical presentation until the child has reached adulthood. Alternatively, there may be differences in the etiology or pathogenesis of pediatric-onset Sjögren syndrome that remove the increased lymphoma risk. For example, the clinical manifestations of Sjögren syndrome in children appear to be different, with less prominent sicca symptoms and more frequent severe systemic manifestations, for example renal tubular acidosis and Devic disease (neuromyelitis optica) [24, 25]. Clearly, further study is needed on the association between malignancy (in particular lymphoma) and childhood-onset Sjögren syndrome.

## Malignancy in Juvenile Dermatomyositis

Malignancy associated with adult dermatomyositis has been reported in 10–30 % of cases [26]. Adenocarcinomas are the most common malignancy, primarily occurring in the lung, ovaries, cervix, gastrointestinal tract, breast, and pancreas. Indeed, the risk of underlying malignancy associated with adult dermatomyositis is sufficient to prompt evaluation for occult malignancy whenever dermatomyositis is diagnosed. The current minimum recommendation is for age, sex, and race-appropriate cancer screening tests and laboratory evaluations, with additional testing directed at specific signs and symptoms. Some propose more invasive screening for malignancy, irrespective of signs and symptoms, but there is currently no consensus on this [26]. Because malignancy risk remains high for three to five years after diagnosis, screening is recommended at six or 12-month intervals during the first two years [27]. In one case series from Korea comparing outcomes of adult and pediatric myositis patients, zero of 16 pediatric patients and six of 48 (13 %) adult patients developed malignancy [28]. Proposed etiologies for this observed association are: a common immunogenic pathogenesis between coexistent dermatomyositis and malignancy, paraneoplastic autoantibodies against muscle fibers, and myotoxic secretions from tumors [28].

There have been no epidemiological studies of the incidence of malignancy associated with juvenile dermatomyositis. The publication of a few single-patient case reports of juvenile dermatomyositis-associated malignancy suggests that there is likely to be an association, but that it is limited to a very small proportion of patients (i.e., fewer than 1 %) [29–31]. An evaluation for underlying malignancy is therefore not considered the standard of care for a typical case of

juvenile dermatomyositis. The reasons for this differing association with malignancy are unclear. There are other features of juvenile dermatomyositis, including the greatly increased propensity to develop dystrophic calcinosis cutis and the greater likelihood of a monocyclic course with eventual disease resolution [32], that indicate it is probably a distinct condition from the adult-onset disease.

## Conclusions

There is probably an increased background malignancy risk associated with JIA. Though less well studied, there is also likely to be an increased risk associated with pediatric-onset SLE. These findings are in general agreement with those found in studies of adults with RA and SLE. Among adults, it seems that disease severity and activity are involved in the subsequent development of malignancy. If this is also true for children, it is conceivable that improved disease control with newer, more effective therapeutic agents may help mitigate the increased risk of malignancy associated with juvenile rheumatic diseases.

The increase in lymphoma risk in pediatric-onset Sjögren syndrome seems to be lower than the marked risk increase seen in adults with Sjögren syndrome, but this association is based upon simple observation and has not been formally studied. Also based on simple observation, the risk of underlying malignancy associated with juvenile dermatomyositis is not as great as in the adult-onset form. These differences in the association with malignancy do not seem to be the only differences between the childhood and adult onset forms of Sjögren syndrome and dermatomyositis. Perhaps improved understanding of the pediatric-onset forms of these diseases will help reveal the pathogenesis underlying the increased risk of malignancy.

To date, rigorous evaluation of the risk of malignancy in pediatric rheumatological disease has been restricted to JIA and has not yet been performed in SLE, Sjögren syndrome, or juvenile dermatomyositis. It is hard to assess the natural course and outcome of pediatric rheumatic diseases from medical records and clinic-based registries, because many patients are transferred from pediatric to adult rheumatology care during the course of their disease. In addition, the incidence of malignancy is very infrequent in childhood—of the order of one per 10,000 person-years. Coupled with the relatively small numbers of children with SLE, Sjögren syndrome, and dermatomyositis, the result is very few outcomes with which to perform robust epidemiological studies. Nevertheless, large multicenter epidemiological studies could further assess the association between chronic inflammation in pediatric rheumatic disease and the development of malignancy both in the pediatric age range and in adulthood.

**Disclosure** Dr Beukelman has served as a consultant for Novartis and Genentech and has received grant support from Pfizer.
Dr Mannion reported no potential conflicts of interest relevant to this article.

## References

Papers of particular interest, published recently, have been highlighted as:
• Of importance

1. Gowdie PJ, Tse SM. Juvenile idiopathic arthritis. Pediatr Clin North Am. 2012;59:301–27.
2. Au K, Reed G, Curtis JR, Kremer JM, Greenberg JD, Strand V, et al. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis. 2011;70:785–91.
3. Smitten AL, Simon TA, Hochberg MC, Suissa S. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther. 2008;10:R45.
4. Franks AL, Slansky JE. Multiple associations between a broad spectrum of autoimmune diseases, chronic inflammatory diseases and cancer. Anticancer Res. 2012;32:1119–36.
5. Onel KB, Onel K. Anti-tumor necrosis factor therapy and cancer risk in patients with autoimmune disorders. Arthritis Care Res (Hoboken). 2010;62:1024–8.
6. Diak P, Siegel J, La Grenade L, Choi L, Lemery S, McMahon A. Tumor necrosis factor alpha blockers and malignancy in children: forty-eight cases reported to the Food and Drug Administration. Arthritis Rheum. 2010;62:2517–24.
7. (FDA) USFaDA. FDA: cancer warnings required for TNF blockers. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm175803.htm. 2009.
8. Lehman TJ. Should the Food and Drug Administration warning of malignancy in children receiving tumor necrosis factor alpha blockers change the way we treat children with juvenile idiopathic arthritis? Arthritis Rheum. 2010;62:2183–4.
9. Cron RQ, Beukelman T. Guilt by association—what is the true risk of malignancy in children treated with etanercept for JIA? Pediatr Rheumatol Online J. 2010;8:23.
10. Thomas E, Brewster DH, Black RJ, Macfarlane GJ. Risk of malignancy among patients with rheumatic conditions. Int J Cancer. 2000;88:497–502.
11. • Simard JF, Neovius M, Hagelberg S, Askling J. Juvenile idiopathic arthritis and risk of cancer: a nationwide cohort study. Arthritis Rheum. 2010;62:3776–82. *By use of national registers, this study was the first published large, rigorous investigation of the association between JIA and incident malignancy, demonstrating a likely increase of background risk.*
12. • Bernatsky S, Rosenberg AM, Oen KG, Duffy CM, Ramsey-Goldman R, Labrecque J, et al. Malignancies in juvenile idiopathic arthritis: a preliminary report. J Rheumatol. 2011;38:760–3. *This study used clinical records from three large pediatric rheumatology practices to identify children with JIA and then evaluate for subsequent malignancy using cancer registers. In contrast with other similar published studies, this study did not find an increased background incidence of malignancy among children with JIA.*
13. • Beukelman T, Haynes K, Curtis JR, Xie F, Chen L, Bemrich-Stolz CJ, et al. Rates of malignancy associated with juvenile idiopathic arthritis and its treatment. Arthritis Rheum. 2012;64:1263–71. *This study used medical claims data to determine the incidence of malignancy associated with JIA and exposure to methotrexate and TNF*

*inhibitors. The authors found an increased background risk of malignancy associated with JIA that was not attributable to exposure to immunosuppressant medication.*

14. Nordstrom BL, Mines D, Gu Y, Mercaldi C, Aquino P, Harrison MJ. Risk of malignancy in children with juvenile idiopathic arthritis not treated with biologic agents. Arthritis Care Res (Hoboken). 2012;64:1357–64.
15. Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006;54:692–701.
16. Smith MY, Sobel RE, Wallace CA. Monitoring the long-term safety of therapies for children with juvenile idiopathic arthritis: time for a consolidated patient registry. Arthritis Care Res (Hoboken). 2010;62:800–4.
17. Chen YJ, Chang YT, Wang CB, Wu CY. Malignancy in systemic lupus erythematosus: a nationwide cohort study in Taiwan. Am J Med. 2010;123:1150.e1–6.
18. Bernatsky S, Boivin JF, Joseph L, Rajan R, Zoma A, Manzi S, et al. An international cohort study of cancer in systemic lupus erythematosus. Arthritis Rheum. 2005;52:1481–90.
19. Parikh-Patel A, White RH, Allen M, Cress R. Cancer risk in a cohort of patients with systemic lupus erythematosus (SLE) in California. Cancer Causes Control. 2008;19:887–94.
20. Bernatsky S, Ramsey-Goldman R, Clarke AE. Malignancy in systemic lupus erythematosus: what have we learned? Best Pract Res Clin Rheumatol. 2009;23:539–47.
21. Bernatsky S, Ramsey-Goldman R, Silverman ED, Duffy CM, Oen K, Rosenberg AM, et al. Cancer risk in pediatric systemic lupus: updated analyses [abstract]. Arthritis Rheum. 2011;63.
22. Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. Arch Intern Med. 2004;164:1275–84.
23. Theander E, Henriksson G, Ljungberg O, Mandl T, Manthorpe R, Jacobsson LT. Lymphoma and other malignancies in primary Sjögren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis. 2006;65:796–803.
24. Tucker LB. Sjögren syndrome. In: Cassidy JT, Petty RE, Laxer RM, Lindsley CB, editors. Textbook of pediatric rheumatology. 6th ed. Philadelphia: Saunders Elsevier; 2011. p. 458–65.
25. Singer NG, Tomanova-Soltys I, Lowe R. Sjögren's syndrome in childhood. Curr Rheumatol Rep. 2008;10:147–55.
26. Aggarwal R, Oddis CV. Paraneoplastic myalgias and myositis. Rheum Dis Clin North Am. 2011;37:607–21.
27. Drake LA, Dinehart SM, Farmer ER, Goltz RW, Graham GF, Hordinsky MK, et al. Guidelines of care for dermatomyositis. American Academy of Dermatology. J Am Acad Dermatol. 1996;34:824–9.
28. Na SJ, Kim SM, Sunwoo IN, Choi YC. Clinical characteristics and outcomes of juvenile and adult dermatomyositis. J Korean Med Sci. 2009;24:715–21.
29. Solomon SD, Maurer KH. Association of dermatomyositis and dysgerminoma in a 16-year-old patient. Arthritis Rheum. 1983; 26:572–3.
30. Martini G, Calabrese F, Biscaro F, Zulian F. A child with dermatomyositis and a suspicious lymphadenopathy. J Rheumatol. 2005;32:744–6.
31. Falcini F, Taccetti G, Trapani S, Lippi A, Bartolozzi G. Acute lymphocytic leukemia with dermatomyositis-like onset in childhood. J Rheumatol. 1993;20:1260–2.
32. Rider LG, Lindsley CB, Cassidy JT. Juvenile dermatomyositis. In: Cassidy JT, Petty RE, Laxer RM, Lindsley CB, editors. Textbook of pediatric rheumatology. 6th ed. Philadelphia: Saunders Elsevier; 2011. p. 375–413.