This study investigated the frequency of and predictive factors for autoimmune lymphoproliferative syndrome (ALPS) in children with lymphoma, chronic immune cytopenia, and nonmalignant organomegaly. Thirty-four children with suspected ALPS (n=13, lymphoma; n=12, immune cytopenia; n=9, nonmalignant organomegaly) were included. Double-negative T-cells, lymphocyte apoptosis, and genetic findings were analyzed. Patients were stratified into two groups as proven/probable ALPS and clinically suspected patients according to the ALPS diagnostic criteria. Of the 34 patients, 18 (53%) were diagnosed with proven/probable ALPS. One patient had a mutation (c.652-2A>C) in the FAS gene. The remaining 16 (47%) patients were defined as clinically suspected patients. Predictive factors for ALPS were anemia and thrombocytopenia in patients with lymphoma, splenomegaly and lymphadenopathy in patients with immune cytopenia, and young age in patients with nonmalignant organomegaly. ALPS may not be rare in certain risk groups. Our study indicates that screening for ALPS may be useful in children having lymphoma with cytopenia at diagnosis, in those having nonmalignant organomegaly with immune cytopenia, and in those having chronic immune thrombocytopenic purpura or autoimmune hemolytic anemia with organomegaly developing during follow-up.

Keywords: Autoimmune lymphoproliferative syndrome, Immune cytopenia, Lymphoma

Bu çalışmanın amacı malign olmayan organomegali, kronik immün sitopeni ve yeni tanı lenfomalı çocuklarda otoimmün lenfoproliferatif sendrom (OILS) sıklığını ve belirleyici faktörlerini araştırmaktır. Bu çalışmada OILS şüpheli 34 hasta dahil edildi (13 hasta lenfoma, 5 hasta otoimmün hemolitik anemi, 7 hasta kronik immün trombositopenik purpura ve 9 hasta malign olmayan organomegali). Çift negatif T-hücreler, lenfosit apoptozis ve genetik bulgular analiz edildi. Hastalar OILS tanı kriterlerine göre kesin ve yüksek olasılıklı OILS’li hastalar ve klinik şüpheli OILS’li hastalar olarak iki gruba ayrıldı. Çalışmaya dahil edilen 34 hastanın, 18’i (%53) kesin ve yüksek olasılıklı OILS’di. Malign olmayan organomegalisi olan bir çocukta FAS geninde mutasyon (c.652-2A>C’yi saptandı. Klinik şüpheli hasta 16 (%47) idi. OILS için belirleyici faktörler; lenfomalı hastalarda anemi ve trombositopeni, kronik immün sitemonii hastalarda splenomegalii ve lenfadenopati; malign olmayan organomegalisi olan hasta adolesan yaş idi. OILS belirli risk gruplarında nadir olmayabilir. Çalışmamız, ilk tanida sitopenisi olan lenfomalı çocuklarda, immün sitopenisi olan nonmalign organomegalii çocuklarda ve izlem sırasında organomegalii gelişen kronik immün trombositopenik purpura ve otoimmün hemolitik anemili çocuklarda OILS taramasının yararlı olabileceğini işaret etmektedir.

Anahtar Sözcükler: Otoimmün lenfoproliferatif sendrom, Immün sitopeni, Lenfoma

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Kaya Z. et al: ALPS in Chronic Immune Cytopenia and Lymphoma

Introduction
Autoimmune lymphoproliferative syndrome (ALPS) is characterized by nonmalignant organomegaly, immune cytopenia, and an increased risk for lymphoma, as well as mutation in the FAS-mediated apoptotic pathway [1,2,3,4,5,6,7,8,9,10]. Few studies have considered the identification of ALPS in certain populations, such as patients with Evans syndrome or lymphoma [11,12,13,14,15,16].

The aim of the present study was to investigate the frequency and predictive factors of ALPS in children with recently diagnosed lymphoma, chronic nonmalignant organomegaly, and chronic immune cytopenia.

Materials and Methods
In total, 34 consecutive patients were included in this study with a two-stage cross-sectional design: those with nonmalignant organomegaly, chronic immune thrombocytopenic purpura (cITP), or autoimmune hemolytic anemia (AIHA) (n=21) between March 2011 and April 2013, and those with newly diagnosed lymphoma (n=13) between June 2013 and March 2015. Patients were also stratified into two groups as proven/probable ALPS (Group 1, n=18) and clinically suspected patients (Group 2, n=16) according to the ALPS diagnostic criteria [17] (Figure 1). The institutional review board approved the study.

Serum vitamin B12 (>1500 ng/L) and immunoglobulin levels, soluble FAS ligand (>200 pg/mL), and interleukin (IL)-10 levels (>20 pg/mL) were measured. Double-negative T-lymphocytes (DNTs; CD3+ T-cell receptor (TCR) αβ+ CD4-, and CD8- DNTs ≥2.5% of the patient’s CD3+ lymphocyte count) were analyzed by flow cytometry [17]. Apoptotic cells were detected by flow cytometry using annexin V-FITC [18]. Nine exons of the FAS gene were analyzed by Sanger sequencing. Data analysis was performed using SPSS 15.0.

Results
The demographic data for ALPS are summarized in Table 1. Of the 34 patients enrolled, 18 (53%) fulfilled the diagnostic criteria for proven ALPS (n=13; 38%) or probable ALPS (n=5; 15%) in Group 1. The remaining 16 (47%) were clinically suspected patients in Group 2. There were significant differences in terms of age between Group 1 and Group 2 (p<0.05). The median age of the patients with nonmalignant organomegaly in Group 1 was significantly lower than that of the nonmalignant organomegaly patients in Group 2 (3 vs. 10 years; p<0.05). The proportions of patients with splenomegaly and lymphadenopathy were significantly higher among the cITP and AIHA subgroups in Group 1 than among the cITP and AIHA subgroups in Group 2 (p<0.05). The proportions of patients with anemia and thrombocytopenia were significantly higher among the lymphoma subgroups in Group 1 than among the lymphoma subgroups in Group 2 (p<0.05).

All relevant data of the 18 patients with proven and probable ALPS are given in Table 2. Of them, 7 (38%) had lymphoma, 5 (28%) had nonmalignant organomegaly, 4 (22%) had cITP, and 2 (12%) had AIHA. Of the seven children with lymphoma, histopathological examination revealed five with Hodgkin lymphoma. Only two of them were positive for Epstein-Barr virus (EBV). Heterozygous splicing mutation in the FAS gene (c.652-2A>C in intron 7) was identified in Case 10 as shown in Table 2. The FAS mutation rate was found to be 20% among patients with nonmalignant organomegaly (n=5).

Five of the 18 children in Group 1 had been scheduled for splenectomy for massive splenomegaly. Splenectomy was canceled after the diagnosis of ALPS. Three of them responded to steroids and mycophenolate mofetil (MMF), one was unresponsive to steroids and MMF but responded to sirolimus, and one received an allogeneic stem cell transplantation. The

Figure 1. Flow chart of the study participants.
ALPS: Autoimmune lymphoproliferative syndrome; NMO: nonmalignant organomegaly; cITP: chronic immune thrombocytopenic purpura; AIHA: autoimmune hemolytic anemia.
remaining seven patients with lymphoma received chemotherapy. Four patients with cITP received mostly on-demand treatment with either steroids or IVIG. Two patients with AIHA received steroids and rituximab, which initially controlled the anemia. MMF was given to both patients who were diagnosed with cITP and AIHA (Cases 13 and 17 in Table 2).

Predictive Factors for ALPS

Presence of anemia (odds ratio [OR]: 3.2; 95% confidence interval [CI]: 1.0–11.4) and thrombocytopenia (OR: 4.2; 95% CI: 1.4–27.2) in patients with newly diagnosed lymphoma, presence of splenomegaly (OR: 4.1; 95% CI: 1.2–13.2) and lymphadenopathy (OR: 7.0; 95% CI: 1.1–42.1) in patients with chronic immune cytopenia, and young age (OR: 2.0; 95% CI: 3.4–12.9) in patients with nonmalignant organomegaly were identified as predictive factors for ALPS.

Discussion

Patients with ALPS have heterogeneous phenotypes that can mimic malignancy and infectious or autoimmune diseases. Long-term follow-up studies demonstrated ALPS mutation in 15% and 85% of involved subjects [3,7,8,9,10]. In this study, proven or probable ALPS was recorded in 53% of suspected patients. However, the FAS mutation rate was found to be 20% among patients with nonmalignant organomegaly.

Lymphadenopathy and splenomegaly are the most common clinical signs of ALPS, as described in our study [19]. Most patients with type Ia develop lymphoproliferation at a median age of 1.8 years [20]. The same clinical pattern was also described incidentally in a 1-year-old girl with FAS mutation in our study. However, the median age at presentation was 4.9 years in patients with undefined ALPS type III [20]. Accordingly, we found the median diagnostic age as 3 years in undefined ALPS patients.
Table 2. The clinical and laboratory findings and outcomes in proven and probable patients with autoimmune lymphoproliferative syndrome.

| No. | Age/ gender | LAP/ SPM | Primary diagnosis | ALPS criteria | Biopsy | FAS mut. | DNT (%) | Defective apoptosis | sFASL (pg/mL) | Vit B12 (ng/L) | IL-10 (pg/mL) | IgG (mg/dL) | Hb (g/dL) | ANC (mm$^3$) | Platelets (10$^9$/µL) | Direct Coombs | Therapy | Outcome |
|-----|-------------|----------|------------------|---------------|---------|----------|---------|-------------------|---------------|----------------|---------------|--------------|-----------|--------------|-----------------|-----------------|---------|---------|
| 1   | 12/boy     | +/+      | HL                | Proven        | +       | -        | 5.0     | Yes               | 170           | 425            | 11           | 1280        | 12         | 41800        | 76200          | -                 | Chemotherapy      | Alive     |
| 2   | 5/boy      | +/+      | NHL               | Proven        | +       | -        | 7.3     | Yes               | 185           | 1281           | 116          | 1200        | 7          | 14000        | 41700          | -                 | Chemotherapy, auto-HSCT | Dead     |
| 3   | 18/girl    | +/-      | HL                | Proven        | +       | -        | 3.5     | Yes               | 189           | 1164           | 10.9         | 3058        | 9          | 3340         | 128000         | -                 | Chemotherapy      | Alive     |
| 4   | 18/girl    | +/-      | HL                | Proven        | +       | -        | 6.9     | Yes               | 201           | 1038           | 11.3         | 2446        | 8          | 4930         | 119000         | -                 | Chemotherapy      | Alive     |
| 5   | 17/girl    | +/-      | HL                | Proven        | +       | -        | 4.6     | Yes               | 180           | 226            | 11.3         | 1300        | 9          | 3000         | 250000         | -                 | Chemotherapy      | Alive     |
| 6   | 11/boy     | +/-      | NHL               | Proven        | +       | -        | 8.4     | Yes               | 177           | 1650           | 11.5         | 2580        | 8          | 15600        | 149000         | -                 | Chemotherapy, auto-HSCT | Alive     |
| 7   | 6/boy      | +/+      | HL                | Proven        | -       | -        | 5.4     | Yes               | 177           | 345            | 11.5         | 1950        | 7          | 2150         | 306000         | -                 | Chemotherapy      | Alive     |
| 8   | 6/boy      | +/-      | NMO               | Proven        | +       | -        | 25.0    | Yes               | 215           | 841            | 21           | 1040        | 12         | 7400         | 111000         | +                 | Steroids, MMF      | Alive     |
| 9   | 3/boy      | +/-      | NMO               | Proven        | +       | -        | 14.2    | Yes               | 180           | 495            | 9.5          | 566         | 10         | 540          | 192000         | +                 | Steroids, MMF, sirolimus | Alive     |
| 10  | 1/boy      | +/-      | NMO               | Proven        | +       | +        | 6.2     | Yes               | 1000          | 1500           | 200          | 2500        | 9          | 1200         | 36000          | +                 | Steroids, MMF      | Alive     |
| 11  | 2/boy      | +/-      | NMO               | Proven        | +       | -        | 19.1    | Yes               | 174           | 460            | 13           | 6090        | 7          | 7300         | 84700          | +                 | Steroids, MMF, allo-HSCT | Alive     |
| 12  | 4/boy      | +/-      | NMO               | Probable      | +       | -        | 7.4     | No                | 179           | 353            | 13           | 2089        | 2          | 1440         | 29100          | +                 | Steroids, MMF      | Alive     |
| 13  | 15/boy     | +/-      | ITP               | Proven        | -       | -        | 6.8     | Yes               | 180           | 312            | 13           | 1080        | 11         | 4800         | 3900           | +                 | Steroids/IVIG, MMF | Alive     |
| 14  | 13/boy     | +/-      | ITP               | Proven        | -       | -        | 6.5     | No                | 174           | 379            | 9.3          | 1518        | 12         | 683          | 39200         | -                 | Steroids/IVIG     | Alive     |
| 15  | 17/boy     | +/-      | ITP               | Probable      | +       | -        | 6.3     | No                | 175           | 421            | 22.1         | 1310        | 16         | 2980         | 25700          | -                 | Steroids/IVIG     | Alive     |
| 16  | 14/boy     | +/-      | ITP               | Probable      | -       | -        | 6.5     | No                | 175           | 311            | 10           | 1570        | 12         | 4900         | 85700          | +                 | Steroids/IVIG     | Alive     |
| 17  | 13/boy     | +/-      | AIHA              | Proven        | +       | -        | 3.7     | Yes               | 187           | 1027           | 9.6          | 583         | 8          | 1340         | 13300          | +                 | Steroids, rituximab | MMF       | Alive     |
| 18  | 6/boy      | +/-      | AIHA              | Probable      | -       | -        | 12.7    | No                | 175           | 1010           | 10.5         | 1579        | 9          | 1210         | 194000         | +                 | Steroids, rituximab | Alive     |

LAP: Lymphadenopathy; SPM: splenomegaly; HL: Hodgkin lymphoma; NHL: non-Hodgkin lymphoma; NMO: nonmalignant organomegaly; DNT: double-negative T lymphocytes; Hb: hemoglobin; ANC: absolute neutrophil count; MMF: mycophenolate mofetil; HSCT: hematopoietic stem cell transplantation; IVG: intravenous immunoglobulin.

Approximately 3- to 4-fold more likely of anemia and thrombocytopenia in lymphoma patients with ALPS was found as 12 years in our study. The median age of lymphoma patients in both adults and children with ALPS was determined to be 12 years in our study [15,16]. Similarly, our patients were mostly diagnosed with Hodgkin lymphoma, EBV, and EBV in addition, children with newly diagnosed lymphoma with the presence of EBV in addition, children with newly diagnosed lymphoma with the presence of EBV in both cases [15,16]. Most reported patients with ALPS have had lymphoma at a median age of 17 years in both adults and children with ALPS [8]. However, the median age of lymphoma patients with biopsy was found to be 12 years in our study [7,8].

Platelet findings indicate that patients with ALPS in chronic immune cytopenia and lymphoma at a median age of 17 years in both adults and children with ALPS was found as 12 years in our study. The median age of lymphoma patients in both adults and children with ALPS was determined to be 12 years in our study [15,16]. Similarly, our patients were mostly diagnosed with Hodgkin lymphoma, EBV, and EBV in addition, children with newly diagnosed lymphoma with the presence of EBV in both cases [15,16]. Most reported patients with ALPS have had lymphoma at a median age of 17 years in both adults and children with ALPS [8]. However, the median age of lymphoma patients with biopsy was found to be 12 years in our study [7,8].
to develop ALPS. Our study indicated that the presence of anemia and thrombocytopenia in patients with lymphoma at diagnosis may be useful for ALPS screening.

Splenectomy and rituximab are not recommended in ALPS because of sepsis and recurrence risk in most cases [1,2,3,21,22,23,24]. We canceled the scheduled splenectomies for five patients with massive splenomegaly. Furthermore, some patients with cITP and AIHA might be resistant to standard treatment, as in previous reports [25,26]. Partial response to rituximab was observed in cases of AIHA. We believe that treatment response could help the physician reach a possible diagnosis of ALPS in children with cITP, AIHA, and nonmalignant organomegaly. The major limitations of the present study were that the other ALPS-related genes [27,28,29,30] were not studied due to lack of resources and all lymphoma cases/adult cases were not included.

Our data indicate that investigation of ALPS is warranted in children with lymphoma presenting with cytopenia, in cases of chronic nonmalignant organomegaly with immune cytopenia, and probably in patients with cITP and AIHA developing organomegaly during follow-up.

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Ethics
Ethics Committee Approval: The Institutional Review Board of the Medical School of Gazi University approved the study.

Informed Consent: The parents of all participants gave informed consent.

Authorship Contributions
Design: Z.K., M.I.; Data Collection or Processing: Z.K., M.I., S.K., F.G.P., Ü.K.; Analysis or Interpretation: N.O., U.B., L.M.A., M.J.D-M., R.R-G., P.G.U., E.Ü.B.; Writing: Z.K.

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