Identification of anti-prothrombin antibodies in the anti-phospholipid syndrome that display the prothrombinase activity

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Abstract

Objective. Prothrombin (PT) is one of the most important antigenic targets for aPL antibodies; however, the prothrombotic mechanism of anti-PT (aPT) antibodies in APS is not fully clarified. Considering that some autoantibodies possess the enzymatic activity, the aim of this study was to test the hypothesis that some aPT antibodies in APS may display prothrombinase activity.

Methods. Six APS patient-derived PT-reactive monoclonal antibodies (mAbs) were analysed for prothrombinase activity on PT. One mAb with prothrombinase activity was examined for its proteolytic activity on PT. In addition, IgG was purified from plasma samples positive with IgG aPT antibodies, and their prothrombinase activity analysed.

Results. Initial analysis of six mAbs revealed that, upon incubation with PT, IS6 mAb displayed prothrombinase activity and catalysed the proteolysis of PT to fragments. Analysis of plasma samples revealed that 9/21 (42.8%) APS patients had IgG antibodies against PT, based on a cut-off value equal to mean +3 S.D. of the level in 21 normal controls. Importantly, of those samples positive for IgG aPT antibodies, two polyclonal IgG (P1 and P2) also displayed prothrombinase activity.

Conclusions. In this study, we showed that some aPT antibodies displayed prothrombinase activity. Such catalytic aPT antibodies may contribute to thrombosis in APS.

Key words: Anti-phospholipid syndrome, Autoantibodies, Prothrombin, Prothrombinase.

Introduction

APS is an autoimmune disorder characterized by thrombosis events and/or fetal loss, and the presence of aPL antibodies [1–5]. aPL antibodies are heterogeneous and recognize a variety of antigens including various phospholipids (PLs), PL-binding proteins and protein–PL complexes [6–17]. Of these plasma proteins, β₂ glycoprotein I (β₂GPI) and prothrombin (PT) are recognized either as the major antigenic targets or as necessary cofactors for aPL antibodies. Antibodies against β₂GPI and its complexes with cardiolipin (CL) probably account for most of the positive findings in tests for anti-CL (aCL) antibodies in APS [18], whereas anti-PT (aPT) antibodies and anti-β₂GPI antibodies are responsible for the majority of the LAC activity [7, 8, 19, 20].

The human coagulation cascade is composed of four major events that occur following the loss of vascular integrity: vascular constriction; platelet activation and aggregation; coagulation cascade and clot formation; and clot dissolution. The coagulation cascade is initiated by expression of tissue factor (TF) upon vascular injury. TF binds and accelerates the activation of coagulation factor VII (FVII), and the activated factors VII (FVIIa) form complexes with TF (designated TF-VIIa), which, in turn, activate FIX and FX (generating FXa and Fxa, respectively). Subsequently, FXa works with FVa to convert PT to thrombin, which then converts fibrinogen to...
a fibrin clot [21, 22]. Since thrombin is the key enzyme in the coagulation cascade, excess thrombin production would promote vascular thrombosis.

Catalytic antibodies are antibodies that hydrolyse their antigenic molecules; therefore, such antibodies are also called antibody enzymes or abzymes. In 1986, two groups [23, 24] first reported such antibodies that bound to the stable transition state analogues. Subsequently, catalytic autoantibodies against coagulation factor VIII (FVIII) were found in patients with haemophilia A, and these antibodies catalysed proteolysis of FVIII [25, 26]. In addition, catalytic anti-platelet autoantibodies were found to cause platelet fragmentation in HIV-related immune thrombocytopenia [27]. Furthermore, catalytic autoantibodies against myelin basic protein were recently reported in 77% of patients with multiple sclerosis [28].

Previously, to explore the prothrombotic mechanism of aPT antibodies, Thiagarajan et al. [29] screened a panel of 34 Bence Jones proteins for prothrombinase activity and found two light chains with the activity. Characterization of one light chain showed that it cleaved PT to two fragments of 55 and 38 kDa [29]. Combined, these findings prompted us to hypothesize that some aPT antibodies may display prothrombinase activity. To test this hypothesis, we analysed some monoclonal and polyclonal aPT antibodies for their enzymatic activity on PT.

Materials and methods

Patient-derived mAb

Six mAbs were used (CL1, -15, -24, IS3, -4 and -6). Their reactivity with PT and other characteristics have been published previously and are summarized in Table 1 [10, 30–33]. Since all mAbs are IgG3, a human monoclonal IgG3 (Calbiochem/EMD Bioscience, La Jolla, CA, USA) was used as a normal IgG control.

Patients and healthy controls

Twenty-one APS patients (16 females and 5 males) and 21 age-matched healthy controls (10 females and 11 males) were enrolled in the present study. All patients satisfied the Sydney classification criteria for definite APS [5]. The average age at the time of blood sampling from APS patients was 35 (range 10–66) years. Anti-β2GPI and aCL antibodies were detected by commercial ELISA, and LA activity was determined by the dilute Russell’s viper venom time (dRVVT) test with a platelet neutralization procedure. As shown in Table 2, 20 (95.2%) patients were positive for IgG aCL (mean 69.1 GPL; range 19–94 GPL) (normal range 0–14 GPL); 2 (9.5%) patients positive for IgM aCL (mean 53.5 MPL; range 25–82 MPL) (normal range 0–14 MPL); 6 (28.6%) patients positive for IgG anti-β2GPI (mean 33.5 U/ml; range 32–38.2 U/ml) (normal range 0–19 U/ml); and 9 (42.9%) patients positive for LA (normal range of dRVVT ratio 0.8–1.2). In addition, most patients (19/21) met the ACR revised criteria for SLE. Informed consent was obtained, and the study was approved by the Research Ethics Committee of National Taiwan University Hospital.

ELISA for antibodies against PT

The ELISA for aPT antibodies was performed as described previously [10]. Briefly, 96-well high-binding plates (Costar, Cambridge, MA, USA) were coated with

| TABLE 1 Summary of the characteristics of six IgG prothrombin-reactive mAb from two APS patients |
|---------------------------------|--------|--------|--------|--------|--------|--------|
| Antigens | CL1 | CL15 | CL24 | IS3 | IS4 | IS6 |
| CL/bovine serum | + | + | + | + | + | + |
| Human PT | + | + | + | + | + | + |
| IgG subtypes | IgG3 | IgG3 | IgG3 | IgG3 | IgG3 | IgG3 |
| Prothrombotic activities | Thrombus | Size | – | + | + | + | + |
| | Duration | – | + | + | + | + | + |

| The reactivity with antigens are from Hwang et al. [10], Zhao et al. [30] and Zhu et al. [31], and are given as + or –. | The antigen used to generate CL1, -15, -24, IS3 and -4. | The antigen used to generate IS6. | The IgG subtypes of six mAbs are from Zhao et al. [30] and Zhu et al. [31]. | The prothrombotic activities are from Pierangeli et al. [32] and Vega-Ostertag et al. [33], and are given as + or –. |
either human PT (from Haematologic Technologies, Essex Junction, VT, USA) at a concentration of 5 μg/ml in Tris-buffered saline (TBS; 50 mM Tris–HCl, 150 mM NaCl, pH 7.5). After incubating overnight at 4 °C, plates were blocked with TBS containing 0.3% gelatin. Then, the tested plasma samples (1/100 dilution), or purified IgG (10 μg/ml, which was determined to be in the linear range of titration curves, or indicated concentrations) in TBS/0.1% gelatin, were distributed into wells in duplicate and incubated for 1.5 h at room temperature. A pooled normal human IgG (Jackson ImmunoResearch, West Grove, PA, USA; or Immune Globulin, Bayer, USA) was used as a normal human IgG control. After washing with TBS, bound human IgG was detected with HRP-conjugated goat anti-human IgG (γ-chain specific; Sigma, St Louis, MO, USA), and the peroxidase substrate tetramethylbenzidine (Kirkegaard & Perry Laboratories, Gaithersburg, MD, USA). Results were read at a wavelength of 450 nm against a background of 650 nm with a VERSAmax microplate reader (Molecular Devices, Sunnyvale, CA, USA). Since IS6 is an IgG aPT mAb, it was then used at 1 μg/ml in each ELISA plate to serve as a reference antibody in the plasma assays. To standardize ELISA results from different assays at different times, the optical density (OD) of each test sample was divided by the OD of IS6 on the same plate and expressed in reference units (RU). Therefore, 1 RU is equivalent to 1 μg/ml of IS6 IgG aPT mAb.

Since some SLE patients may have antibodies that bind to gelatin, plasma samples were analysed simultaneously for binding to wells that were coated with either an autoantigen (i.e. PT) or buffer only, and then blocked with TBS/0.3% gelatin. Then, for each test sample, its IgG binding to gelatin-only wells (i.e. coated with buffer only) was subtracted from its IgG binding to the antigen (PT)-coated wells, and the differential binding was expressed as IgG aPT antibodies.

Affinity purification of IgG from plasma samples

Polyclonal IgG was purified from patients’ plasma samples that were positive for IgG aPT antibodies, using HiTrap Protein G columns (Pharmacia, Piscataway, NJ, USA) according to the manufacturer’s instructions.

Functional analyses of the prothrombinase activity of antibodies on PT

The prothrombinase activity of antibodies was analysed in buffer (50 mM Tris–HCl, 150 mM NaCl, 5 mM CaCl2, 0.1% polyethylene glycol 8000, pH 7.4) in 96-well microtitre plates. Briefly, 50 μl of human PT (100 nM) were separately incubated with 50 μl of a test mAb (200 μg/ml or indicated concentrations), purified IgG of patients (2 mg/ml), a pooled normal human IgG or an IgG3 mAb isotype control for 18 h at 37 °C. Subsequently, to each reaction mixture 50 μl of the thrombin-specific chromogenic substrate S-2238 was added (H-D-Phe-Pip-Arg-p-nitroanilide, 450 μM; Chromogenix, Molndal, Sweden). Generation of p-nitroaniline was monitored by measuring OD at 405 nm over time by a VERSAmax microplate reader. The activity of thrombin was determined as rates of hydrolysis of S-2238 in the linear range of absorbance at 405 nm.

SDS–PAGE analysis of PT cleavage by the IS6 mAb

To characterize the proteolytic activity of IS6, PT at the indicated concentrations was pre-incubated with IS6 or IgG controls in TBS containing 5 mM CaCl2 and 0.1% polyethylene glycol 8000 for 18 h at 37 °C. After incubation, 20 μl of each sample was subjected to SDS–PAGE in a 10% gel under reducing conditions. The separated proteins were stained by Coomassie blue.

Statistical analysis

The mean RU plus 3 s.d. of 21 healthy controls was used as the cut-off, and plasma samples with RU values higher than the cut-off were considered positive. The comparisons between APS patients and normal controls were conducted using the Mann–Whitney U-test. Differences in binding activity of polyclonal IgG and antibody-induced activity of thrombin were analysed using analysis of variance followed by the Bonferroni multiple comparison test. When IS6 was analysed alone with the IgG3 mAb control, Student’s t-test was used. A two-tailed P-value of < 0.05 was considered as statistically significant.

Results

Functional analyses of patient-derived IgG monoclonal aPT antibodies on generating thrombin-like activity

To test our hypothesis that some aPT antibodies in APS patients may possess prothrombinase activity, we first analysed the effects of patient-derived mAb towards generation of thrombin-like activity. To date, six patient-derived monoclonal aPL antibodies had been shown to react with PT [10], including one aPT antibody (IS6) and five aCL antibodies (CL1, -15, -24, IS3 and -4) (Table 1). As can be seen in Fig. 1A, incubation of IS6 with PT led to substantial thrombin-like activity. In contrast, no increased thrombin-like activity was detected when PT was incubated with other mAbs, a monoclonal IgG3 isotype control or a polyclonal IgG control. The final concentrations of IS6 and PT (before adding the thrombin substrate) were 100 μg/ml (0.67 μM) and 50 nM, respectively. Of note, the plasma concentrations of IgG and PT are 10 mg/ml (67 μM) and 100 μg/ml (1.4 μM), respectively [34].

Importantly, IS6 alone did not directly hydrolyse chromogenic substrate S-2238 (Fig. 1A). Moreover, the IS6-induced thrombin-like activity was stable over a period of 3 h, as the accumulated substrate conversion in the presence of IS6 increased constantly over those in the presence of an IgG3 control mAb (Fig. 1B).

Assuming that IgG aPT antibodies in an APS patient account for ~1% of the total IgG, the IS6 concentration of 100 μg/ml would approach total IgG aPT antibodies. We therefore studied the prothrombinase activity of IS6 at a series of 2-fold lower concentrations (from 100 to 6.25 μg/ml). The results showed that incubation of
PT with IS6 at 25 \( \mu \text{g/ml} \) led to the generation of significant thrombin-like activity (Fig. 1C).

**SDS–PAGE analyses of the mixture of IS6 and PT**

To determine the mechanism by which incubation of IS6 with PT led to generation of thrombin-like activity, IS6 was incubated with PT at various concentrations, and the mixtures were then analysed by SDS–PAGE. The final concentrations of IS6 and PT were 100 \( \mu \text{g/ml} \) and 0–1 \( \mu \text{M} \), respectively. As shown in Fig. 2A, besides the three expected bands of PT (70 kDa) and IS6 (50 kDa gamma chain and 25 kDa light chain), there were three additional bands with molecular sizes of 49, 36 and 27 kDa (designated as fragment A, B and C, respectively). Of them, fragment B (36 kDa) is likely to correspond to thrombin or pre-thrombin [35] and may possess the enzymatic activity.

Of note, IS6 alone (in lane 1) and PT alone (in lanes 2, 4 and 6) had only the expected bands, indicating that neither protein was contaminated with any unknown protease and that there was no detectable autolysis of PT under the same condition. In addition, incubation of PT with control human IgG did not yield any additional band (Fig. 2B). Combined, these data indicated that IS6 catalysed the proteolysis of PT.

**Detection of IgG aPT antibodies in some APS patients**

To generalize the significance of the above findings, we used a previously described ELISA for aPT antibodies [10] to analyse plasma samples from 21 APS patients and 21 healthy controls. All samples were analysed at the 1/100 dilution. As shown in Fig. 3A, the levels of plasma IgG aPT antibodies in APS patients were significantly higher than those in healthy controls [RU values: mean (S.D.), 0.5 (0.15) vs 0.28 (0.07); \( P < 0.0001 \)]. Using the mean \( +3 \text{S.D.} \) in healthy controls as the cut-off, IgG aPT antibodies were found in 9/21 (42.8\%) APS patients. Of these nine patients, all had positive IgG aCL antibodies, four were positive for LA and four were positive for IgG anti-\( \beta_2 \text{GPI} \) antibodies.

A concern was raised that the observed IgG aPT antibodies might actually reflect IgG aPL antibodies that bound to PL, which first bound to PT, as PT contains the \( \gamma \)-carboxyglutamic acid domain that mediates binding to PL [36]. To address this possibility, IgG purified from three plasma samples positive for aPT antibodies (designated as P1, P2 and P3) was analysed for their binding to PT. Bound IgG was measured and expressed in
Fig. 2 The IS6 aPT mAb catalyses proteolysis of PT. (A) IS6 was incubated separately with PT at various concentrations (0–1 μM) at 37°C for 18 h, and then the lysates were analysed by gel electrophoresis in a 10% gel under reducing conditions. Lane 1, IS6 alone; lane 2, PT alone at 0.5 μM; lane 3, IS6 + 0.5 μM PT; lane 4, PT alone at 0.75 μM; lane 5, IS6 + 0.75 μM PT; lane 6, PT alone at 1 μM; lane 7, IS6 + 1 μM PT. (B) PT at 1 μM was incubated with either a monoclonal IgG3 isotype control or a polyclonal IgG control, under the same experimental conditions. Lane 1, IgG3 alone; lane 2, PT alone at 1 μM; lane 3, IgG3 + 1 μM PT; lane 4, polyclonal IgG alone; lane 5, PT alone at 1 μM; lane 6, polyclonal IgG + 1 μM PT. All IgG were used at 100 μg/ml.

OD [mean (s.e.m.)]. Figure 3B showed that purified IgG from these three patients bound better to PT than a pooled polyclonal IgG control [P1: 0.137 (0.003); P2: 0.339 (0.003); P3: 0.132 (0.001); IgG control: 0.063 (0.002)] P1 vs control, P2 vs control, P3 vs control, respectively; P < 0.001]. Moreover, Fig. 3C showed that all of them (P1, P2 and P3) bind to PT in a concentration-dependent fashion. Together, these findings indicate the presence of IgG aPT antibodies in some APS patients.

Generation of thrombin-like activity by patient-derived polyclonal IgG

Thereafter, we investigated the functional properties of IgG purified from those plasma samples that were positive for aPT antibodies. Before the tests, the purity of human IgG was evaluated by SDS-PAGE and no contamination of other protein was found (data not shown). The functional assays were carried out similarly to the above experiments, except that polyclonal IgG was used at a final concentration of 1 mg/ml, which was approximately 1/10 of the total plasma IgG. The results showed that incubation of two of nine PT-reactive polyclonal IgGs (P1 and P2) with PT led to generation of thrombin-like activity that was expressed in OD [mean (s.e.m.)] [P1: 0.0795 (0.0001); P2: 0.1461 (0.0014); IgG control: 0.0004 (0.0001) for P1 vs control, P2 vs control, respectively, P < 0.001] (Fig. 4A). Moreover, such thrombin-like activity was stable over a period of 3 h, as the accumulated substrate conversion in the presence of P1 or P2 increased constantly over those in the presence of a polyclonal IgG control (Fig. 4B).

Discussion

To test the hypothesis that some aPT antibodies in APS possess prothrombinase activity, we first analysed six PT-reactive mAbs and found that IS6 displayed prothrombinase activity upon incubation with PT (Fig. 1). A preliminary mechanistic study showed that IS6 catalysed proteolysis of PT to three fragments (Fig. 2). Of note, IS6 had been shown to promote thrombosis in an animal model [33]. Importantly, polyclonal IgGs from two APS patients positive for aPT antibodies (P1 and P2) were also shown to display prothrombinase activity (Fig. 4). Combined, the present studies show that some aPT antibodies in APS patients may catalyse directly generation of thrombin-like activity, resulting in a pro-coagulant state.

In the process of mAb generation, Epstein–Barr virus was first used to transform B cells. Since the virus also activates B cells [37], it is possible that the IS6 hybridomas were generated from resting B cells, which normally do not produce aPT antibodies in patients. Therefore, to determine the pathological relevance of initial findings with IS6, we analysed purified IgG from APS patients for their prothrombinase activity. Figure 4 shows that incubation of polyclonal IgG from two APS patients with PT led to generation of thrombin-like activity. These data demonstrate that catalytic aPT antibodies do exist in some APS patients.

By analysing a panel of 34 Bence Jones proteins (i.e. light chains isolated from patients with multiple myeloma) for prothrombinase activity, Thiagarajan et al. [29] found two light chains with the ability to generate thrombin activity from PT, suggesting a possible mechanism whereby antibodies could induce a pro-coagulant state. However, the antigen specificity of parental antibodies of the positive light chains (Bence Jones proteins) was unknown, and clinical data (especially the thrombosis history) of the host patients were not given [29]. Therefore, the clinical significance of these two light chains with prothrombinase activity is uncertain. In contrast, of one mAb (IS6) and two polyclonal IgGs (P1 and P2) that displayed prothrombinase activity, all react with PT and all are from APS patients with venous and/or arterial thrombosis. IS6 was from a female patient with primary APS, and the two polyclonal IgGs were from two unrelated female patients with APS secondary to SLE.

The plasma concentrations of PT and IgG are 100 μg/ml (1.4 μM) and 10 mg/ml (67 μM), respectively [34]. Along this line, final concentrations of these proteins in the functional assays were 50 nM for PT, 100 μg/ml for
IS6 and 1 mg/ml for purified IgG; all were within normal plasma levels. Moreover, considering that the plasma IgG concentration is $\approx 10$ mg/ml, a concentration of 100 mg/ml represents 1% of plasma IgG. Thus, the observed prothrombinase activity of antibodies in some APS patients is likely to be pathologically relevant.

To date, there is no gold standard assay for LA activity that is 100% sensitive. Therefore, it is advisable to use

**Fig. 3** Serological analyses of patients’ plasma samples for IgG aPT antibodies. (A) Plasma samples from 21 APS patients and 21 healthy controls were analysed at 1:100 dilution for IgG aPT antibodies. The dashed line represents the cut-off, which is mean RU + 3 S.D. of 21 normal controls. Asterisk denotes $P < 0.0001$. (B) Purified IgG from three patients’ plasma samples (positive for IgG aPT antibodies, designated P1, P2 and P3) and a control polyclonal human IgG were analysed at 10 $\mu$g/ml for PT binding. The mean and S.E.M. are given ($n = 2$). Asterisk denotes $P < 0.001$. (C) P1, P2, P3 and a control polyclonal human IgG were analysed at the indicated concentrations for the binding to PT. The mean and S.E.M. are given ($n = 3$).

**Fig. 4** Functional analyses of purified IgG for the prothrombinase activity. The experiments in (A) and (B) were carried out similarly to those in Fig. 1, except that IgG was analysed at 1 mg/ml. The mean and S.E.M. are given ($n = 2$). Asterisk denotes $P < 0.005$. 
two or more tests to determine the presence of LA [5]. In this study, however, LA activity was tested only by dRVVT. That may underestimate the presence of LA in our patients, and may explain why only 9 of 21 APS patients and 4 of 9 patients with aPT antibodies were positive for LA activity.

Recently, increasing attention has been paid to aPT antibodies for their role in thrombosis in APS patients [8, 19, 38–47]. Among these studies, some reported association of aPT antibodies with thrombosis [38, 43, 45], whereas others did not confirm the association [39, 40]. To explore the possible mechanisms by which aPT antibodies may promote thrombosis, Fleck et al. [8] and Permpikul et al. [19] showed that purified aPT antibodies bound to immobilized phosphatidylserine in the presence of Ca\(^{2+}\) and PT; and Rao et al. [44] reported that an LAC IgG preparation could enhance the binding of PT to endothelial cells (ECs) and increase the generation of thrombin in the presence of FXa and FVa. Along this line, Zhao et al. [30] showed that IS6 aPT mAb enhanced the binding of PT to damaged ECs and shortened EC-based plasma coagulation times. These combined data indicated that some aPT antibodies may concentrate PT on cell surface PLs and thus enhance the conversion of PT to thrombin, leading to a hypercoagulant state.

Interestingly, using the same IS6 aPT mAb, Vega-Ostertag et al. [33] showed that incubation of EC with this aPT antibody led to increased expression of E-selectin and TF on ECs. In this context, our current findings provide yet another pro-coagulant mechanism by which aPT Ab may directly catalyse proteolysis of PT and generate a thrombin-like activity. Taken together, these findings show that a single aPT antibody may have multiple pro-coagulant pathways to promote thrombosis in patients. In the future, it will be important to determine the prevalence of aPT antibodies in APS patients with each of the above three pro-coagulant mechanisms.

For the diagnosis of APS, several laboratory tests have been developed that include the detection of LA, aCL antibodies and anti-\(\beta_2\)-GPI antibodies, and the assay of thrombin generation [5, 48]. However, due to the immunological and functional heterogeneity of antibodies in APS, these assays are of incomplete sensitivity and specificity. Like other aPL antibodies, aPT antibodies are also functionally heterogeneous, which may explain, at least in part, the aforementioned conflicting findings regarding the association of aPT antibodies with thrombosis in APS patients [38–40, 43, 45]. Moreover, these heterogeneous properties of aPT antibodies are most likely to render the efforts to assess the clinical significance of aPT antibodies in APS fruitless. Instead, it will first be necessary to define all subsets of aPT antibodies, delineate the PT epitopes recognized by the pathologically important aPT antibodies, and then, to develop specific assays for the detection of APS-relevant aPT antibodies. Hopefully, such assays may clarify the roles of aPT antibodies in thrombosis in APS, and thrombosis in patients may be properly predicted.

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**Rheumatology key messages**

- Autoantibodies against PT are found in some APS patients.
- Some aPT antibodies display prothrombinase activity that may contribute to thrombosis.

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Clinical Vignette

Intramedullary tuberculoma during infliximab therapy

A 39-year-old male with AS treated with infliximab presented us with a progressive radicular pain in the right upper extremity, cervical pain, dry cough and fever. Cervical and spinal MRI revealed intramedullary tumour located at C4 with important oedema (Fig. 1). Cerebrospinal fluid was normal. Gastric aspiration revealed Mycobacterium tuberculosis. CT chest scan showed diffuse, small, nodular changes and lymphadenopathy concluding to a miliary tuberculosis. Anti-tuberculous treatment was begun and corticosteroids therapy was given. Pulmonary and neurological signs and fever progressively decreased.

There is an increased risk of tuberculosis associated with anti-TNF-α therapy. Extrapulmonary forms of tuberculosis are common under anti-TNF-α therapy. TNF-α production is a requirement for formation of granulomas that sequester mycobacteria and prevent their dissemination [1]. This important role of TNF-α in the control of tuberculosis infection partly explains the increased prevalence of reactivation of tuberculosis in patients treated by TNF-α blockers.

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