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Autoinflammatory diseases in children and adults

SP0080 RECURRENT EPISODES OF FEVER AND ARTHRITIS IN ADULT PATIENT

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Background: Familial Mediterranean Fever (FMF) is a relatively rare condition that belongs to the more recent group of autoinflammatory diseases (AIDs)[1]. It primarily affects patients with Mediterranean or Middle Eastern origins and its clinical setting includes short, recurrent episodes of fever, serositis, skin rash and a high risk of amyloidosis[2]. FMF is an autosomal recessive transmitted disease and several mutations of the Mediterranean fever gene (*MEFV*) on chromosome 16 have been identified[3]. Patients respond well to colchicine therapy or if necessary, biological therapy with anti-IL 1, IL6 or anti-TNF could be initiated[4]. Establishing the right diagnosis might raise difficulties for rheumatologists who are not fully accustomed to this condition.
Objectives: To evaluate the clinical course, specific features and treatment difficulties of a male patient diagnosed with FMF in adulthood, based on the description of a case report.
Methods: Case-description using patient's medical records and investigations.
Results: This is the case report of a 37-year old male patient currently admitted for right knee arthritis and high grade fever (39.1℃). His medical history dates back at age 16 when he presented in the Pediatric Department with recurrent episodes of prolonged fever (up to 40℃), diffuse abdominal pain together with myalgia, arthralgia accompanied by increased acute phase reactants; after various sources of infection and hematological malignancies were excluded, physicians noted positive low titer ANA (1/20) but normal complement fractions, absent lupus (LE) cells. Further medical investigations showed a negative rheumatoid factor, ACPA, negative antibodies' panel (dsDNA, Sm, Ro, U1-RNP) and absent cryoglobulins but a positive HLA B27. No signs of sacroiliitis were detected on the x-ray. Patients' repeated complaints of knee or ankle arthritis together with later finding of positive anti-Salmonella and anti-Shigella antibodies leaded to establishing the diagnosis of reactive arthritis. Due to symptoms' persistence and reoccurrence under non-steroidal anti-inflammatory drugs, he was prescribed high dose corticosteroids and sulfasalazine. At age 20 the patient presented with recurrent arthritis of the knees and ankles, fever (38.5℃) and abdominal pain with markedly elevated inflammatory markers. The abdominal ultrasound highlighted a splenomegaly and peritonitis. Colchicine treatment was initiated and his favorable response led to MEFV genetic testing that revealed a mutation of the 10.1 exon, thus confirming the diagnosis of FMF by fulfilling two major criteria of the Tel-Hashomer diagnostic set. Subsequently, he performed a gingival biopsy that excluded the presence of amyloid deposits. Patient's partial response to colchicine with repeated incomplete attacks of FMF and persistent inflammatory syndrome led to the initiation of biological therapy with Etanercept along with Sulfasalazine and glucocorticoids, due to temporary unavailability of an anti-IL1 agent. Patient's delay in diagnosis and longstanding corticosteroid therapy led to major articular consequences (bilateral aseptic osteonecrosis of the femoral head with requiring hip arthroplasty).
Conclusions: This case presentation depicts the hardships of setting the right diagnosis in a case of late onset FMF due to unusual geographical setting, absence of suggestive family history and heterogeneous clinical presentation together with possibilities in therapeutic approach if patients are non or partially responsive to traditional therapies. Furthermore it points out possible drug side effects and comorbidities that require the same quality medical care as the main rheumatic disease.
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Immunogenicity of biologics; myth or reality?

SP0081 THE T CELL RESPONSE TO THERAPEUTIC ANTIBODIES

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Therapeutic antibodies (TMabs) are part of the best successful therapeutic products of the last decades. They are currently used to treat many inflammatory diseases such as rheumatoid arthritis (RA) and bowel diseases and represent worldwide a market of several billions of dollars. However they have the major drawback to be potentially immunogenic and therefore might elicit anti-drug antibodies (ADA). ADA could dramatically reduce the efficacy of the drugs or might provoke allergic reactions. Because generally self-proteins are less immunogenic than foreign proteins, the sequence of therapeutic antibodies has been humanized. However humanization even at the highest level does not fully guarantee the lack of immune responses demonstrating the important need to know more about ADA response. Because T cells are known to initiate the ADA response, we are currently investigating the T cell response to immunogenic therapeutic antibodies. With the perspective of immunogenicity prediction, we quantified the number of very rare T cells specific for therapeutic antibodies in the blood of normal donors and found a good concordance between the number of T cells specific to them and their respective clinical immunogenicity level. We then identified the CD4 T cell epitopes of four immunogenic TMabs with different levels of humanization, namely the chimeric antibodies Infliximab (Ifx) and Rituximab (Rtx), the humanized antibody Natalizumab (Ntz) and the fully human Adalimumab (Adm). CD4 T lymphocytes were expanded by several weekly rounds of stimulation with autologous dendritic cells loaded with each of the investigated antibodies and the T cell specificity was assessed by IFNg ELISPOT using overlapping peptides encompassing the whole sequence of their variable parts. Nine epitopes were identified in the VL and VH chains of Rituximab and Infliximab. They overlap CDR or FR regions of both chimeric antibodies and some of them are shared by multiple donors. As inferred from binding experiments, T cell epitopes often exhibited a good affinity for HLA-DR molecules found in the responding donors. Nine CD4 T cell epitopes were found in the VH and VL parts of the humanized therapeutic antibody Natalizumab while the fully human antibody Adalimumab hosted 10 T cell epitopes. As a result, the number of T cell epitopes is very similar across the different therapeutic antibodies but their location is highly variable from one antibody to another one. Finally to assess the clinical relevance of the identified T cell epitopes, we evaluated the ability of Ifx and Rtx T cell epitopes to stimulate T cells of patients having developed ADA. Two third of the T cell epitopes identified from the healthy donors stimulated PBMCs from ADA+ patients and promoted the secretion of a diversity of cytokines. These data emphasize the predictive value of evaluating the T cell repertoire of healthy donors to anticipate and prevent immunogenicity of therapeutic antibodies. Together our data provide new insights on the origin of immunogenicity of chimeric, humanized and human therapeutic antibodies.
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SP0082 IMMUNOGENICITY OF BIOLOGICS IN INFLAMMATORY BOWEL DISEASES

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Anti-tumor necrosis factor-alpha and anti-integrin monoclonal antibodies show great benefits for inducing and maintaining remission, healing the mucosa and restoring the quality of life of patients with inflammatory bowel diseases. The therapeutic potential of these intrinsically powerful biologicals is tempered by a high variability in clinical response. Whereas primary non-response is defined as the lack of clinical response to treatment, assessed 8–12 weeks after initiation, secondary loss of response is defined as loss of clinical benefit after initially responding which can be attributed to disease-related or drug-related factors. Assays have been developed to determine the concentration of the therapeutic antibody in serum of the treated patient. The trough concentration is the concentration just before the next administration and for practical reasons therapeutic drug monitoring is mainly based on measurement of these trough concentrations. Several studies have reported correlations between through concentration of infliximab, adalimumab, golimumab, vedolizumab and clinical outcome. Optimal therapeutic windows have been defined for both infliximab and adalimumab. A panel of prospective studies in which dosage regimens are adapted in order to achieve target trough infliximab concentrations that correlate with beneficial therapeutic outcomes have been initiated.
Immunogenicity is the capability of biologicals to elicit an unwanted immune response that results in the formation of anti-drug antibodies. Anti-drug antibodies can be non-neutralizing or neutralizing. Non-neutralizing antibodies do not impair the drug-target interaction but may increase clearance of the drug resulting in lower serum concentrations. Neutralizing anti-drug antibodies compete with the target for the antigen-binding site and modulate directly the activity of the drug in addition to the enhanced clearance of the drug. A number of anti-drug antibody assays to quantify the immunogenicity of biologicals have been developed. Most of the assays quantify the total amount of anti-drug antibodies but comparing anti-drug antibody concentrations between different assays is hampered by the