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REVIEW IN GASTROENTEROLOGY

Ipilimumab-induced colitis: A new challenge for gastroenterologists☆

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Abstract Many drugs can produce enterocolitis and they should always be included in the differential diagnosis of this clinical picture. Entities such as antibiotic-associated colitis and neutropenic colitis have been known for some time and recently a new type of drug-induced colitis has emerged due to monoclonal antibodies.

Ipimumab is a humanized monoclonal antibody against the CTLA4 molecule that is involved in the maturation and regulation of T lymphocyte activation. This drug causes immune activation and has an immune-mediated antitumor effect with excellent results in tumours such as melanoma. However, several immune-related adverse effects may occur in different organs. The most frequently involved site is the gastrointestinal tract, with adverse effects ranging from mild diarrhoea to colitis with systemic involvement, intestinal perforation, and even death.

Although no similarities have been found in the pathogenesis with inflammatory bowel disease, treatments have been used in correlation with its autoimmunological profile: anti-TNF alpha corticosteroids have shown clinical efficacy in moderate to severe disease. However the use of anti-TNF treatment has not been defined and the safety profile is unknown. The inclusion of these new therapies in the treatment of several tumours requires familiarity with these entities and their management should be approached as a new challenge for the gastroenterologist.

For that reason, we conducted a review of ipilimumab-induced colitis, evaluating essential features of its symptoms, diagnosis and treatment.

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Colitis secundaria a ipilimumab: un nuevo reto para el gastroenterólogo

Resumen Existen numerosos fármacos de diversas clases que pueden producir enterocolitis y deberían incluirse siempre en el diagnóstico diferencial de este cuadro clínico. Si ya conocíamos entidades como la colitis asociada a antibióticos o la colitis neutropénica asistimos en la actualidad a un nuevo cuadro de colitis inducida por inmunofármacos.

Ipimumab es un anticuerpo monoclonal humanizado que actúa contra la molécula CTLA4, que se encuentra implicada en la regulación de la maduración y activación del linfocito T. Este fármaco ocasiona una activación inmunológica y un efecto antitumoral inmunomediado con excelentes resultados en tumores como el melanoma. Sin embargo, son varios los efectos adversos de tipo inmunomediados que puede producir en distintos órganos, siendo el tubo digestivo uno de los más frecuentes, ocasionando desde una diarrea leve hasta cuadros de colitis con afectación sistémica, perforación intestinal e incluso muertes.

Aunque no se han encontrado similitudes en la patogenia con la enfermedad inflamatoria intestinal dada su base inmunológica se han utilizado terapias en correlación con la misma: corticoides e incluso anti-TNF alfa han mostrado eficacia clínica en cuadros moderados y graves. Sin embargo, las pautas de tratamiento anti-TNF no se encuentran definidas ni conocemos su perfil de seguridad.

La inclusión de estas nuevas terapias en el tratamiento de diferentes tumores nos obliga a conocer estas entidades y afrontar su manejo como un nuevo reto para el gastroenterólogo.

Por este motivo, hemos querido realizar una revisión de la colitis inducida por ipilimumab tratando los aspectos esenciales en la clínica, diagnóstico y terapéutica.

Little is known about the prevalence of drug-induced colitis, and incidence is probably underestimated. Nevertheless, it should always be borne in mind and included in the differential diagnosis of enterocolitis.

Introduction

The compounds most commonly associated with drug-induced colitis are non-steroidal anti-inflammatory drugs (NSAID) and antibiotics, the latter being the cause of the classic *Clostridium difficile*-induced colitis.[1] However, other drug groups have also been associated with colitis caused by various pathogenic mechanisms, such as infection, ischaemia or immune-inflammatory processes; these include lansoprazole, ticlopidine, clozapine, vasoconstrictors, progestogens and various cytotoxic agents used in oncology, such as irinotecan, 5-fluorouracil, capecitabine and docetaxel, among others. Another characteristic clinical condition, neutropenic colitis or typhlitis, has also been associated with the use of these agents.[2,3]

Incidence of drug-induced colitis is growing following the introduction of biological therapies in oncology, where cases of diarrhoea and colitis secondary to administration of different types of drugs such as selective epidermal growth factor receptor inhibitors (cetuximab, panitumumab, erlotinib) and selective vascular endothelial growth factor inhibitors (bevacizumab), as well as antibodies against immune checkpoints, such as anti-cytotoxic T-lymphocyte antigen 4 antibodies (ipilimumab) have been reported.[3,4]

Ipilimumab can cause characteristic and potentially serious colitis. If the current trend towards increased use of this drug in different tumours continues, gastroenterologists will most probably become involved in the management of the disease, which has prompted us to compile this review of the symptoms, diagnosis and treatment of drug-induced colitis.

What is ipilimumab and what is it used for?

Ipilimumab is a human IgG1 monoclonal antibody against cytotoxic T-lymphocyte-associated protein 4 (CTLA4).

T-lymphocyte maturation in the lymph nodes begins with the interaction between the antigen presenting cell (APC) and the T-lymphocyte, involving presentation of the antigen bound to the major histocompatibility complex I (MHC-I) antigen, which must bind to the T-cell receptor. This results in the maturation, activation and proliferation of a specific T-cell clone. This process must be tightly regulated, and requires a second co-stimulatory signal produced when T-cell surface protein CD28 binds to protein B7 on the APC. These 2 signals trigger the immune response with T-cell activation and proliferation in an antigen-specific response.

CTLA4 (CD152) is a type I membrane protein that is expressed on T-lymphocytes and monocytes, and is generally sequestered in intracellular vesicles. Once the immune response has been activated through the mechanisms described, CTLA4 is transported (as a regulatory molecule) to the cell surface of the lymphocyte and binds to proteins of the B7 family expressed on APCs, preventing CD28-B7 complex formation and dampening the amplitude of the initial response.

Ipilimumab blocks the CTLA4 protein by binding to its surface when it is expressed on the membrane. This results