

# Recurrent urinary tract infections and low secretory IgA following CD19-directed CAR T-cell therapy for relapsed acute lymphoblastic leukemia

## To the Editor:

CD19-directed CAR T-cell therapy (CD19-CAR-TCT) has been successful as a novel modality in treating recurrent or refractory B-lineage acute lymphoblastic leukemia (B-ALL).<sup>1,2</sup> Despite absence of circulating B lymphocytes, severe pan-hypogammaglobulinemia, decreased plasma cell (PC) content, and B-cell aplasia in tissues, persistence of some humoral immune response mediated by remaining CD19-negative PC was shown following CD19-CAR-TCT.<sup>3</sup> The authors further emphasized the need for investigating mucosal antibodies in these patients. Our case constitutes an example of a potential CD19-CAR-TCT complication due to impaired secretory immune response.

A 10-year-old female with standard-risk B-ALL started treatment before relocating to the United States in 2011. She also had history of vitamin B12 deficiency from infancy, which later was discovered to be due to hereditary intrinsic factor deficiency.<sup>4,5</sup> She continued treatment, but experienced systemic relapse 22 months from diagnosis while receiving maintenance chemotherapy. She was then treated as per the UK ALL-R3 regimen, but did not achieve complete remission. She underwent matched sibling donor bone marrow transplantation (BMT) and relapsed in the bone marrow 5 months after BMT. Following clofarabine and cytarabine chemotherapy, she developed secondary hemophagocytic lymphohistiocytosis with multiorgan failure. However, she achieved and remained in complete remission for 10 months. Due to prior systemic relapse, she underwent CD19-CAR-TCT at another institution 28 months ago. She has been supplemented with intravenous immunoglobulin regularly and continues to be in remission with undetectable peripheral blood B lymphocytes and serum IgA and IgM levels.

Prior to CD19-CAR-TCT, the patient had three separate urinary tract infections (UTI) secondary to *Escherichia coli* during 40 months of follow up, which clustered in less than a 3-month period and corresponded to the time of BMT when she was on graft-versus-host disease prophylaxis. Both immune suppression and possible incomplete eradication supported by the observation of short intervals between UTI episodes might have contributed to recurrence. She had three UTI episodes 14, 18, and 23 months after CD19-CAR-TCT due to *E. coli* and *Proteus mirabilis* with negative renal/bladder ultrasound and voiding cystourethrography studies. Salivary secretory IgA (sIgA) levels were very low on two measurements at 0.31 and 0.35 (normal: 5–28).


Secretory IgA predominates the immunoglobulin content in secretions and is produced by local stromal or nodal tissue PC along with joining (J) chain, which binds two or more IgA monomers that associates with an epithelial glycoprotein called “secretory component”

facilitating secretion to mucosal surfaces. Monomeric IgA can be also found in mucosal secretions, making 13–17% of the salivary IgA and 77% of the salivary monomeric IgA that is estimated to be serum derived.<sup>6</sup> Secretory IgA is critical in mucosal pathogenic microorganism colonization by preventing bacterial adherence, agglutinating microorganisms, interfering with bacterial motility, and neutralizing bacterial enzymes and toxins.<sup>7</sup> Furthermore, binding of sIgA by *E. coli* protein was shown to inhibit neutrophil activation.<sup>8</sup>

Low urinary tract sIgA has been linked to recurrent symptomatic bacteriuria in females with normal urinary tracts.<sup>9</sup> While salivary sIgA does not directly reflect urine sIgA status, it may suggest possible low sIgA level in the urine. Thus, low salivary sIgA should warrant testing sIgA levels in the urine given the nature of humoral immunodeficiency associated with CD19-CAR-TCT in such cases.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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