Case Report
Development of acute lymphoblastic leukemia in a patient with increased hematogones after toxic bone marrow damage

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Abstract: To the best of our knowledge we describe the first case showing the association of increased B cell precursors/hematogones in a regenerating post-toxic bone marrow with subsequent development of a B-ALL. Since all immunohistochemical/moleculargenetic analyses have failed to identify the initial malignant leukemic clone, we suggest a close-meshed follow-up of such cases to identify potential mechanisms for the malignant transformation of B-cell precursors/hematogones and to prevent further fatal courses.

Keywords: Bone marrow, toxic damage, hematogones, B-ALL

Case Report

A 44 year old male patient without former history of pulmonary/haematological diseases suffered in December 2008 from a severe bronchopneumonia and sepsis accompanied by a peripheral trizytopenia (1a) and toxic bone marrow (BM) damage (1b) possibly due to a Viagra derivate containing sildenafil/tadalfil. Notably, a ~5% TDT/CD34/PAX5+ cell population detectable in BM (1b inset) was interpreted to be the occurrence of increased reactive B-cell precursors/hematogones in regenerating haematopoiesis due to its loose distribution and immunohistochemical/moleculargenetic phenotype (lack of CD54 or CD123 coexpression [1], [2] (1c); polyclonal rearrangement of the framework 3a region (FR3a) of the immunoglobuline heavy chain (IgH) genlocus (inset 1c)).

Three months later the patient showed complete clinical recovery with normalized blood values (2a) and hematopoiesis (2b) but an even increased TDT/CD34/PAX5+ fraction in BM (~20%; 2b inset) with identification of single TDT/CD54+ blasts (2c) and a clonal Fr3a/IgH rearrangement on a polyclonal background (2c inset). Inspite of the un conspicuous clinical picture a preleukemic phase of an acute B-lymphoblastic leukemia (B-ALL) was suggested that became clinically apparent after additional two months (CD10/CALLA positive; t(9;22) and t(4;11) negative) showing abundant blasts in peripheral blood (3a) and BM (3b) with coexpression for CD54 (3c) and detection of a monoclonal Fr3a/IgH rearrangement (3c inset).

The association of increased B cell precursors/hematogones in regenerating post-toxic BM with subsequent development of a B-ALL has so far not been described. Although it remains unclear whether toxic bone marrow damages by sildenafil/tadalfil or sepsis were involved in the development of this case of acute leukemia, all immunohistochemical/moleculargenetic analyses have obviously failed to identify the initial malignant leukemic clone demonstrating the necessity of a close-meshed clinical follow-up of such cases to prevent further fatal courses and to identify potential mechanisms for the malignant transformation of B-cell precursors/hematogones as described previously [3], [4].
Toxic bone marrow damage followed by B-ALL

Figure 1. Peripheral blood smear (1a) and bone marrow biopsy (1b) from December 2008 showing a distinct pancytopenia (1.6x10⁶/µl red blood cells (RBC), 0.5x10³/µl WBC (white blood cells) and 7.8x10⁴/µl PLT (platelets)) as well as classical histological aspects of toxic bone marrow damage with vanished and edematous marrow areas (1b). Approximately 5% loosely distributed TDT positive bone marrow cells were identified by immunohistochemistry (IH) (inset 1b) and double immunofluorescence staining (DIF) (1c) without coexpression of the cell adhesion molecule CD54 [1], [2] (1c) and detection of a polyclonal rearrangement of the FR3a/2a-IgH genlocus (inset 1c).

Figure 2. In March 2009 both normalized blood values (2a) with regular blood cells in peripheral blood smear (2a) and regularly maturing hematopoiesis in normocellular bone bone marrow spaces (2b) were detectable. By contrast ~20% TDT positive cells were found by IH (inset 2b) with partial coexpression of TDT and CD54 in DIF (2c) and detection of a prominent peak in the amplification of Fr3a/IgH rearrangement (inset 2c) corresponding to a clonal rearrangement/cell population on a still existing polyclonal background (2c inset).

Figure 3. In May 2009 a distinct leucocytosis (3a; 45x10³/µl) became apparent with abundant blasts in peripheral blood (3a) and bone marrow (3b). In IH (inset 3b) and DIF (3c) the blasts were strongly positive for TDT and showed a homogenous coexpression of TDT and CD54 (3c) as well as a prominent monoclonal rearrangement of the Fr3a/IgH genlocus (inset 3c).

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