TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Letter to the Editor

Turk J Med Sci
(2015) 45: 742-744
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doi:10.3906/sag-1408-149

Myelodysplastic features and cellular senescence in autoimmune disorders: a pilot study on patients with collagen tissue disorders and immune thrombocytopenic purpura

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Received: 31.08.2014 • **Accepted/Published Online:** 24.11.2014 • **Printed:** 30.06.2015

To the Editor:

Dysplastic findings in blood cells arise due to any challenge during the course of normal differentiation and can be encountered in autoimmune disorders (1–3).

Some myelodysplastic findings closely overlap with features of cellular senescence, which may be dependent on or independent of telomeres. The latter case is due to severe DNA damage, oncogenes, oxidative stress, and strong mitogenic signals (4).

No hallmark of senescence has been identified yet. Salient features of senescent cells are: 1) permanent growth arrest (generally in G1); 2) increased cell size and polyploidy; 3) expression of senescence-associated β-galactosidase (SA-β-gal) activity; 4) expression of p16INK4a in some of them, which causes reorganization of heterochromatin as punctate highly condensed domains of facultative heterochromatin [(senescence-associated heterochromatin foci (SAHF)] that silence critical proproliferative genes; 5) DNA damage response (DDR), which initiates and maintains the senescence growth arrest; and 6) secretion of growth factors, proteases, and cytokines by senescent cells with persistent DDR signaling (senescence-associated secretory phenotype) (5). Alterations in cell cycle and reorganization in the genome is accompanied by altered cytokinesis, karyokinesis, cellular scaffolding and alterations in cell morphology, formation of micronuclei (6) or fragmented nuclei, flattened cell shape, and intracellular vacuoles (7–9).

Herein, we aimed to investigate the coexistence of cellular senescence with myelodysplastic findings in patients with juvenile rheumatoid arthritis (JRA, n = 2), systemic lupus erythematosus (SLE, n = 1), acute immune thrombocytopenic purpura (ITP, n = 1) and chronic ITP (n = 1). SLE and chronic ITP patients were not on any therapy for at least 45 days; the others were at first admission (age: 11.6 ± 4.61 years; 2 females, 3 males; controls: 13.66 ± 4.16). The leukocytes were prepared and stained by SA-β-gal (8).

All patients had dysmorphic blood cells on blood smears (up to 80% vs. 25% in the controls). The leukocytes of all patients displayed positive SA-β-gal staining (by 33%–57% vs. 0% in the controls) (Figure 1) .

In our patients, we could not test all features of cellular senescence, but not all senescent cells express all possible senescence markers (5). In our patients, SA-β-gal positivity, increased cell size and increased chromatin clumping, which mimics nuclear fragmentation (10), and SAHF are compatible with cellular senescence.

We think that the proinflammatory cytokines and chemokines in SLE, JRA-PT, and ITP patients (11–13) led to cellular senescence (14) by keeping the immune system in a state of chronic low-level activation and giving rise to immunosenescence through loss of telomeres with each S phase (5), which was increased by inflammatory mediators that are secreted by senescent cells themselves (14). Additionally, destruction of tissue environment and stem cell niches (14) by inflammatory mediators, proteases, and immune cells may have exacerbated aging through hematopoietic stem cell dysfunction, altered mitosis, and dysmorphism.

Essentially, decline in absolute number of T (CD8+, CD4+) and B lymphocytes (15) in immunosenescence, abnormal telomere/telomerase system in ITP (16), and accelerated loss of T cells in juvenile idiopathic arthritis (17) were reported.

In conclusion, these results suggest that cellular senescence plays a role in the pathogenesis of autoimmune disorders and myelodysplastic features may be a reflection of cellular senescence. Further studies are needed for confirmation.

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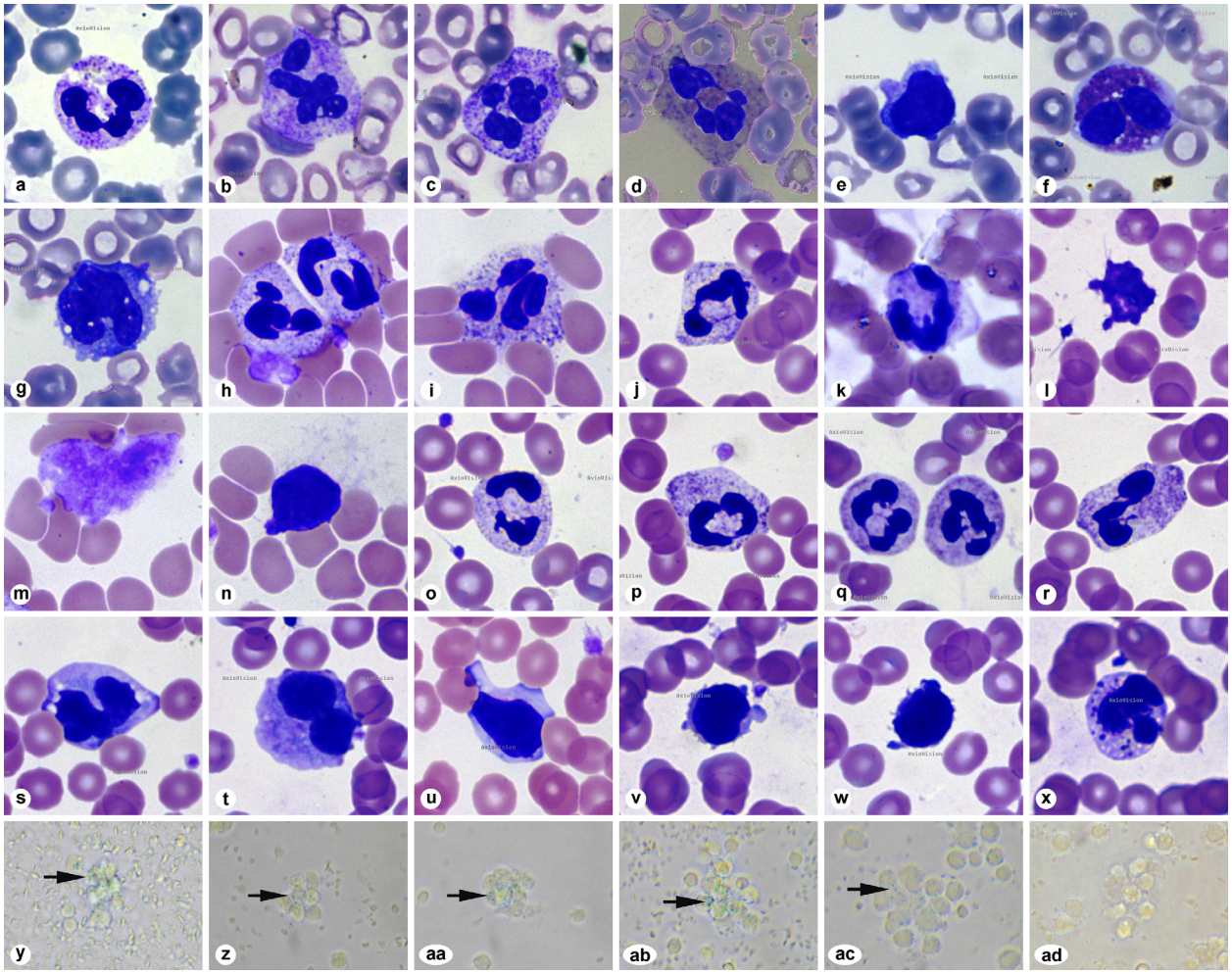

Figure 1. Dysmorphic hematological features of the peripheral blood smears of patient ASİ with chronic ITP **(a–g)**, patient MEY with JRA **(h–n)**, and patient TÇ with JRA **(o–x)**.
Neutrophils: Macropolycytes (neutrophil of ≥15 μm) **(b, c, h, i)**, hypersegmentation **(c)**, cytoplasmic vacuoles **(a)**, hypogranulation **(d, o)**, cytoplasmic protrusions with or without granules **(h, k)**, irregular distribution of granules **(a, c, j)**, abnormal nuclei with nucleic protrusions **(q, r)**, neutrophils with long chromatin between the nuclei **(j, o)**, pseudo-Pelger–Huet cells **(o, p)**. Lymphocytes: Cytoplasmic protrusions **(e, n, u, v, w)**. Basophils: Centralization of granules **(f)**, abnormal nuclei and hypogranulation **(x)**. Monocytes: Abnormal nuclei **(g, s, t)**, cytoplasmic vacuoles **(g, s)**, cytoplasmic protrusion **(g)**. Platelets: Big or giant platelets **(l, m)**. **β**-Gal staining photographs of the patients: Patient TÇ with JRA **(y)**, patient MBY with JRA **(z)**, patient KÇ with SLE **(aa)**, patient HA with acute ITP **(ab)**, patient ASİ with chronic ITP **(ac)**, and control **(ad)** (100×).

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