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LETTER TO THE EDITOR

How to resolve a clinical and molecular puzzle: concomitant monoclonal gammopathy of undetermined significance (MGUS) with neutrophilia and clonal hematopoiesis of indeterminate potential (CHIP)

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Dear Editor,

The association between plasma cell (PC) neoplasms (PCN) and neutrophilia is a rare but well-known phenomenon [1–3]. CHIP designates asymptomatic presence of clones in the peripheral blood and/or the bone marrow carrying somatic mutations of genes, typically mutated in myeloid neoplasms, with a not exactly predictable risk of progression towards cancer, bearing analogies to MGUS and monoclonal B-lymphocytosis [4, 5]. We report on a patient with concomitant MGUS, neutrophilia, and CHIP, rising questions of the nature of neutrophilia in PCN as well as caveats of overinterpretation due to the simultaneous co-existence of MGUS and CHIP.

A 60-year-old Caucasian male presented with fatigue and splenomegaly in 2008. Blood counts showed leukocytosis with mature neutrophilia [leukocytes of 32 g/L (reference, 4-12 G/L) with 90% neutrophils (28.8 G/L)]. Immunofixation electrophoresis revealed IgG_{κ} monoclonal gammopathy (13.1 g/L (reference, 0.7–1.6 g/L)) without CRAB criteria. The bone marrow biopsy was hypercellular with increased maturing myelopoiesis and with 5% kappa-restricted PC (Fig. 1a–c). Neither mutations of *JAK2* and *CSF3R* nor *BCR-ABL1*-, *PDGFRA*, *PDGFRB*, or *FGFR1* rearrangements were detected. The neoplastic PCs were CD38+/CD138+/CD19−/CD20−/CD56− on flow cytometry. No PCN-characteristic structural genomic alterations could be detected. Exome sequencing (Illumina) and targeted re-sequencing (IonTorrent) on purity-controlled sorted cells showed identical mutations of *DNMT3A* [c.2287_2288insGGCG, p.(Val763GfsTer2)], *TET2* [c.3879_3880insTAC, p.(Tyr1294dup)], and others (Fig. 1d) in the neutrophilic population (CD66+), in the PC (CD138+)—containing the kappa-restricted clone—and in the stem cell pool (CD34+). Consequently, we suspected clonal relationship between the neutrophilic and the PC population and even a putative common progenitor. However, we also noted that the mutations were present at similar allelic frequencies in the sorted, purified cell pools but also in their negatives (in each CD138−, CD66−, or CD34− pool), indicating a distinct clonal outgrowth represented equivalently in the background of each sorted and left-over cell populations. Based on this, the hypothesis of an additional pan-hematopoietic/pluripotent clone giving rise to approximately 15 to 20% of all neutrophils and PCs (most probably not the MGUS PCs) was set up. This hypothesis was sustained by the high prevalence of *TET2* and *DNMT3A* mutations, which are very characteristic of CHIP [6]. Finally, the diagnosis of MGUS with associated mature neutrophilia and a co-existent pan-hematopoietic CHIP was established. The patient remained asymptomatic showing no significant disease progression for 10 years, which further strengthened our interpretation.

The nature of neutrophilia in PCN is not fully understood [7]. It may be secondary to abnormal cytokine production by the neoplastic PCs [8, 9]. This is substantiated by one case showing elevated G-CSF levels in the serum and PC positivity on immunohistochemical stains [8] and appears to be a plausible paraneoplastic mechanism. In other reported cases, mutations of *JAK2*, *SETB2*, or *CSF3R* have been detected [1, 9], suggesting the possibility of concurrent chronic neutrophilic leukemia (CNL) and PCN. In our case, supported by the absence of *CSF3R* driver mutations and by the indolent clinical course, the diagnosis of MGUS with paraneoplastic neutrophilia and independent CHIP has been established, in line with the growing evidence that somatic mutations in hematopoietic cells with clonal expansions can be acquired with aging [4]. The originality of our case resides

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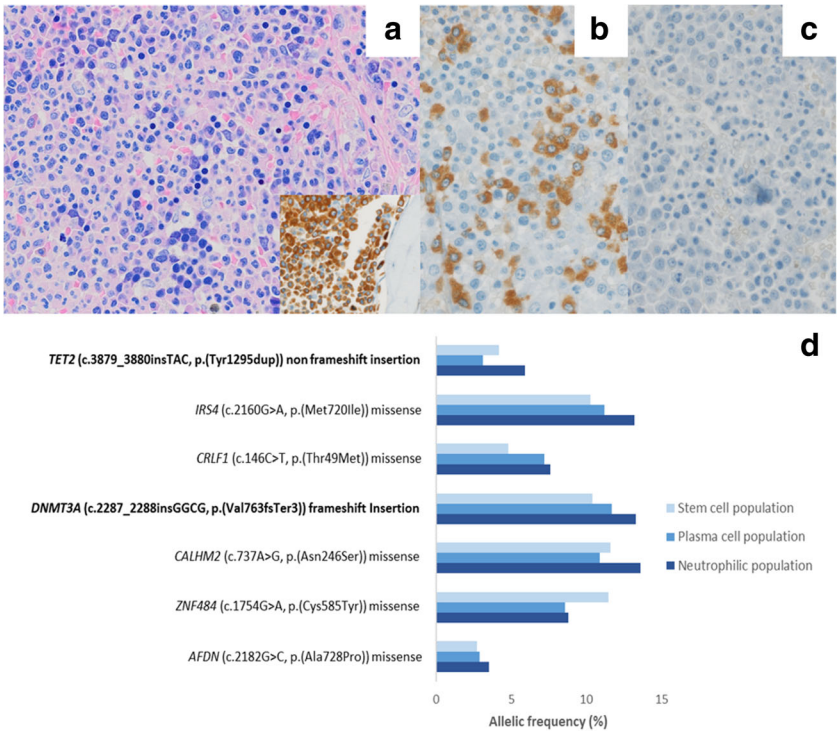

Fig. 1 **a** Medium-power (× 200) view of the Giemsa-stained bone marrow biopsy showing increased myelopoiesis without signs of dysplasia, nor increased numbers of myeloblasts, but with intermingled plasma cells. Insert: immunostaining for myeloperoxidase (× 200).**b**, **c** Interstitial plasmacytosis showing kappa light chain restriction (**b** = kappa, **c** = lambda; × 360, immunoperoxidase). **d** Non-silent somatic mutations detected by the whole exome sequencing applied to sorted populations of neutrophils (CD66+), plasma cells (CD138+), and hematopoietic stem cells (CD34+). Mutations in *DNMT3A* and *TET2* most likely represent clonal hematopoiesis of indeterminate potential (CHIP) and are equally present in all three populations. These mutations are accompanied by mutations in other genes, the significance of which is unknown. The variant allelic frequencies of the detected mutations are compatible with a scenario of their co-occurrence in one clonal stem cell population giving rise to various offsprings

in the simultaneous co-existence of two clonal, pre-malignant, but clonally unrelated disorders: MGUS and CHIP. It also illustrates difficulties of interpreting expanding molecular data. Finally—to reflect the value of a holistic approach in diagnostics—only integration of clinical (absence of disease progression) and molecular findings (CHIP-type mutations along with their allelic frequencies in the sorted cell populations) made it possible to resolve this challenging instance.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of informed consent Written informed consent was obtained from the patient.

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