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LETTER TO THE EDITOR

Coincidence of lymphomatoid granulomatosis, chronic myelomonocytic leukemia, and anaplastic T cell lymphoma after methotrexate therapy for rheumatoid arthritis

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Dear Editor,

We present a 79-year-old male with seronegative polyarthritis (RA) and three different neoplasms of myeloid and lymphoid origin. He was treated with methotrexate (MTX) (15 mg) weekly and prednisolone (15 mg) daily for 2 years and 4 months. The development of lymphoproliferative diseases (LPDs) including various types of lymphomas is reported to be associated with the use of MTX for the treatment of RA [1, 2].

The first diagnosis of RA was done on 11/2011. Since 9/2013, arthritis of the left wrist was seen. Three cycles of steroids were given intraarticularly. Infection with herpes zoster was diagnosed in 9/2013. An increased swelling of the left wrist with increased inflammatory levels was reported in 3/2014 (Fig. 1a, b).

The first neoplasm was lymphomatoid granulomatosis (LyG) of the wrist rendered in 3/2014. In the lesion of the wrist, typical necrosis and angiocentric/angio-destructive growth and CD30- and EBV-positive blasts were observed. The neoplastic cells were positive for CD20, CD79alpha, and Pax5. The second neoplasm was a myelodysplastic/myeloproliferative neoplasm of chronic myelomonocytic leukemia (CMML) type with mild proliferation of monoblasts (< 5%) in 6/2016. The neoplastic cells were positive for CD14, CD163, lysozyme, and CD68. The third neoplasm was an anaplastic lymphoma kinase-negative large cell lymphoma (ALCL), in 6/2016. The β chain of the T cell receptor in this ALCL was monoclonal. The immunoglobulin heavy chain and the γ chain of the T cell receptor were polyclonal. The neoplastic cells were positive for CD3, CD4, and CD5. They were negative for CD18, CD15, CD20, CD79a, Pax5, CD10, CD23, CD117, CD123, S100, and tryptase (Fig. 1c–e).

Panel sequencing for *ASXL1*, *BRAF*, *CALR*, *CBL*, *CSF3R*, *DNMT3A*, *EZH2*, *FLT3*, *IDH1*, *IDH2*, *JAK2*, *KIT*, *KRAS*, *MPL*, *NPM1*, *NRAS*, *RUNX1*, *SETBP1*, *SRSF2*, *TET2*, *TP53*, and *U2AF1* was performed for all three lesions, as well as for peripheral blood, and the oral mucosa. Percentages of cells harboring the *SRSF2* mutation of (p.P95H) were LyG 33.1%, CMML (bone marrow) 51.5%, peripheral blood 52%, and ALCL 14.2%. Percentages of cells harboring the *TET2* mutation of (p.C1378R) were LyG 87.7%, CMML (bone marrow) 94%, peripheral blood 99.2%, and ALCL 61.7%. The high allelic burden of *TET2* and *SRSF2* mutations in the lymphoid neoplasm argues clearly against contamination of the lymphoid neoplasms by infiltrating myeloid cells and is an evidence for the presence of these mutations in the lymphoma cells. There was no germline mutation as shown by sequencing of the cells from the oral mucosa. On the basis of this data, we conclude that a common stem cell with *SRSF2* and *TET2* mutations gave rise to three different neoplasms of the myeloid and lymphatic lineages.

Several studies have implicated hematopoietic stem cells (HSCs) as a primary reservoir for the accumulation of mutations [3]. The incidence of *TET2* gene alterations in various myeloid diseases ranges between 10 and 25% [4]. *TET2* loss is known to confer increased self-renewal to stem cells and leads

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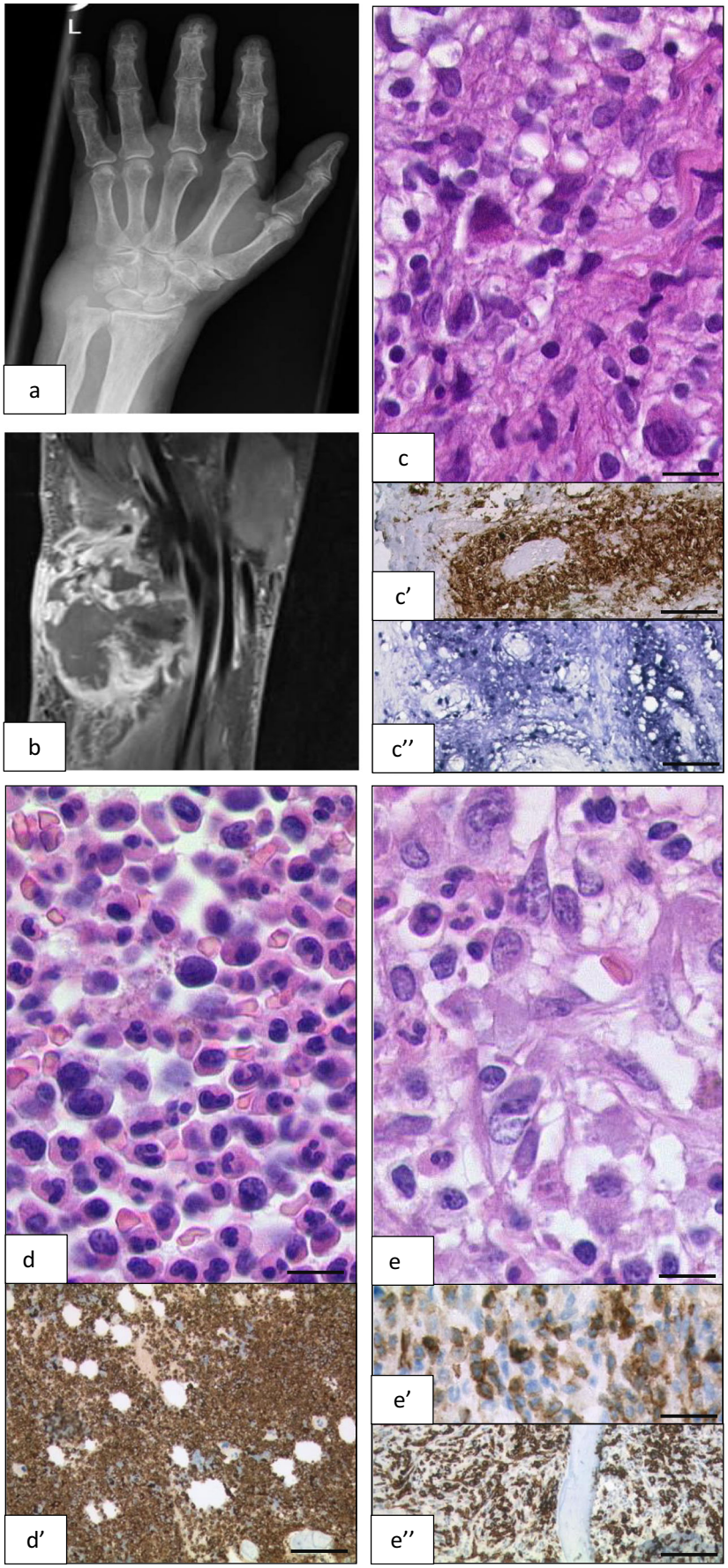
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Fig. 1 The radiography of the left hand, histology, and immunohistology. (**a**) The X-ray demonstrates a soft tissue swelling of the lateral wrist without any osseous destruction. (**b**) The MRI of the wrist (T1-w spin-echo sequence with fat saturation following contrast media administration) shows a large mass within the wrist laterally. The mass shows signs of a central large necrosis and a vital periphery with some vital central septal formations on 3/2014. (**c**) LyG. (**d**) CMML. (**e**) ALCL. Hematoxylin-eosin staining of the three neoplasms. (c') Immunostaining with an antibody against CD30. (**c**") EBER in situ hybridization. (**d**') Immunostaining with an antibody against lysozyme. (**e**') Immunostaining with an antibody against CD4. (**e**") Immunostaining with an antibody against CD30. Bars represent 15 μm (**a**, **d**, **e**); 50 μm (**a**', **a**", **d**' and **e**"); 25 μm (**e**'). (Microscope-Zeiss Axiophot, Camera-JVC KY-F75U)

to the myeloproliferation of *SRSF2* (serine/arginine-rich splicing factor 2) which is important for splice-site selection and spliceosome assembly, and both constitutive and alternative splicing. Recently, recurrent somatic mutations involving the RNA splicing machinery were identified in a substantial proportion of patients with myelodysplastic syndrome (MDS) [5].

In conclusion, we describe a unique case of a patient receiving MTX for seronegative polyarthritis, who developed three different malignancies of myeloid and lymphoid origin with two oncogenic mutations in common.

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Authorship Contributions T.F.E.B., H.K., A.R., U.L., P.M., and R.E. designed the research and analyzed and interpreted data. T.F.E.B. and R.D. wrote the manuscript.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All the performed methods and experiments were in line with the guidelines of the ethics committee of the Federal General Medical Council. Informed consent was obtained from the individual included in the study.

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