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Short Commentary

Short Commentary on "*TP53* and *PTEN* Mutations were shared in Concurrent Germ Cell Tumor and Acute Megakaryoblastic Leukemia"

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ABSTRACT

Concurrent mediastinal Germ Cell Tumors (mGCTs) and hematological malignancies in the same patient have been reported in 2-3% of extragonadal GCT cases. In most cases, the involved GCTs are non-seminomatous and mediastinal, while the Hematological Malignancies (HMs) are often acute megakaryoblastic leukemia. Isochromosome 12p has been frequently detected in both tumors. Recently, two cases of concurrent mGCT and acute myeloid leukemia harboring *TP53* and *PTEN* mutations were reported. We published our research article about the case of a 37-years old male patient with concurrent GCT and acute megakaryoblastic leukemia. Similar to previous studies, *TP53* and *PTEN* mutations were shared in both tumors, in addition to the other seven shared mutations. This suggests that the concurrent occurrence of GCTs and HMs are associated with a common founding clone with a characteristic coexistence of *TP53* and *PTEN* mutations.

Keywords: Acute myeloid leukemia; Germ cell tumor; *TP53*; *PTEN*

DESCRIPTION

We provide a short commentary on our previously published article titled "*TP53* and *PTEN* Mutations Were Shared in Concurrent Germ Cell Tumor and Acute Megakaryoblastic Leukemia," which highlighted the presence of a founding clone with *TP53* and *PTEN* mutations. This founding clone potentially developed two concurrent malignancies of the mediastinal Germ Cell Tumor (mGCT) and Acute Megakaryoblastic Leukemia (AMKL) in one patient [1].

GCTs are the most common malignancies among adolescent males with approximately 2-5% of GCTs occurring in the extragonadal site. Among them, mGCTs occur predominantly within the anterior mediastinum. Although clinical characteristics differ between mGCTs and testicular GCTs, the lack of cytogenetic differences suggests that both are derived from gonadal lesions [2]. Since 1985, approximately 60 cases have reported a possible association between mGCTs and Hematological Malignancies (HMs) [3,4]. In a large, international, multicenter database study including 635 patients with extragonadal GCT, HMs were observed in 17 extragonadal GCTs, with 6% incidence rate of concurrent mGCT and HM [5]. In most cases, the involved GCTs were non-seminomatous and mediastinal, while the HMs were predominantly AMKL. The prognosis of patients with mGCTs and associated HMs is extremely poor, with a median overall survival of 5 months [6]. Historically, chromosomal analysis used to analyze the pathogenesis of these concurrent tumors has elicited frequent presence of isochromosome 12p in both tumors. This finding suggests that HMs and mGCTs potentially arise from common progenitor cells because isochromosome 12p is the most common chromosomal abnormality in GCTs, but is rare in AML without mGCT association [5-8]. However, the mechanism of concomitant disease development was still largely unknown.

Recently, by utilizing whole-exome sequencing, two cases of concurrent mGCT and AML were found to have *TP53* and *PTEN* mutations [9,10]. Interestingly, in our case, as the same result in previous two cases, loss-of-function mutations of *TP53* and *PTEN* were shared in both tumors, in addition to the other seven shared mutations. These three cases suggest that the coexistence of GCTs and HMs may be a biologically unique entity arising from a common founding clone with characteristic concomitant genomic aberrations of *TP53* and *PTEN*. *TP53* mutations have been widely observed in a variety of tumors, including AML, although they are uncommon in GCT [11]. Similarly, *PTEN* mutations have mostly been reported in a number of tumors, except in AML [12]. Mice with heterozygous *PTEN* deletion demonstrated genomic instability and the development of multiple spontaneous tumors. The simultaneous deletion of *TP53* and *PTEN* in mice promoted tumor genesis and metastasis [13], and its molecular mechanisms might reflect the pathology and dismal prognosis of the concurrent disease of mGCT and AML.

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In our case, variant allele frequency values suggest that the initiator clone was formed by four mutations (*TP53*, *PTEN*, *RLF*, *DLG2*, and *YY2*) and developed by accumulation of the following four mutations (*PCLO, GOLGA8J, EDRF1,* and *ASF1A*) (Figure 1).

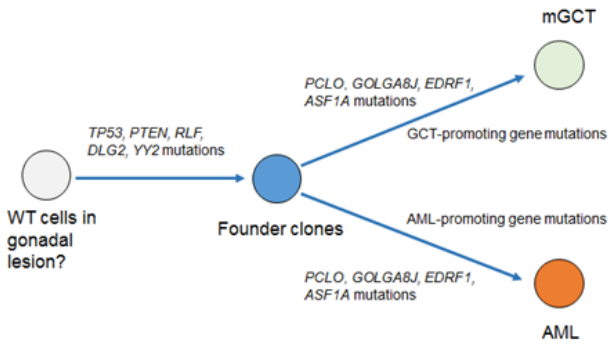

Figure 1: A model of tumor evolution of concurrent mediastinal Germ Cell Tumors (mGCTs) and Acute Myeloid Leukemia (AML) in the same patient. AML: Acute Myeloid Leukemia; mGCTs: mediastinal Germ Cell Tumors; WT: Wild Type

Subsequently, one subclone with GCT-promoting gene mutations and another subclone with HM-promoting gene mutations may develop from the initiator clone, resulting in the development of both tumors. Because the interval between the onset of mGCT and development of HM is usually less than 6 months, we suspect that mGCT-associated HMs develop by a mechanism different from that of general treatment-associated secondary AML or myelodysplastic syndromes which typically develop after a year of exposure to cytotoxic drugs. In these concomitant diseases, a preleukemic clone, with both *TP53* and *PTEN* mutations, was possibly selected and expanded early following treatment with GCTs, resulting in rapid development of AML.

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