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Prolonged QTc interval as a side effect of concomitant administration of CDK4/6 inhibitor and cytochrome P-450 enzyme inhibitors

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A 45-year-old woman was diagnosed with metastatic breast cancer (BC) with dissemination to the bones and mediastinal lymph nodes of the. Taking into account the biological type (luminal B, HER2 negative) and the low dynamics of the disease the best therapeutic option was to use hormone therapy in combination with cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor. The therapy consisting of CDK 4/6 inhibitor - in combination with a selective oestrogen receptor downregulator – fulvestrant was initiated in July 2021. Additionally, due to the premenopausal status luteinizing hormone-releasing hormone analogue was administered. Pre-treatment electrocardiogram (ECG) was normal (fig.1). On day 15th the patient was seen for the purpose of therapy continuation. The control ECG showed: bradycardia – heart rate 54/min. and QTc- 502 msec (fig. 2). The patient revealed that due to dysphagia that was a new symptom she underwent gastroscopy a week earlier (revealing white deposits covering 30% of the esophageal mucosa) and was diagnosed with esophageal mycosis. Oral nystatin suspension QID and fluconazole 50 mg tablets QD were administered on the day of gastroscopy. Due to persisting dysphagia antifungal agents were continued for the next ten days, together with hormonal therapy. However, due to significant risk of ventricular arthythmia the CDK 4/6 inhibitor was interrupted. Control ECG performed 3 weeks later was normal and the CDK 4/6 therapy was restarted.

Protein kinase inhibitors- commonly used in oncology molecularly targeted drugs are cardiotoxic and can cause various disorders of the cardiovascular system. This group of agents includes CDK 4/6 inhibitors that occasionally prolong the OTc interval [1]. Cyclin-dependent kinase 4/6 inhibitors are metabolized by CYP3A enzymes and inhibit CYP3A themselves. Co-administration with a strong CYP3A inhibitor (e.g. fluconazole) increases cardiotoxicity of CDK 4/6 inhibitors and should be avoided [2].

Conflict of interest: none declared

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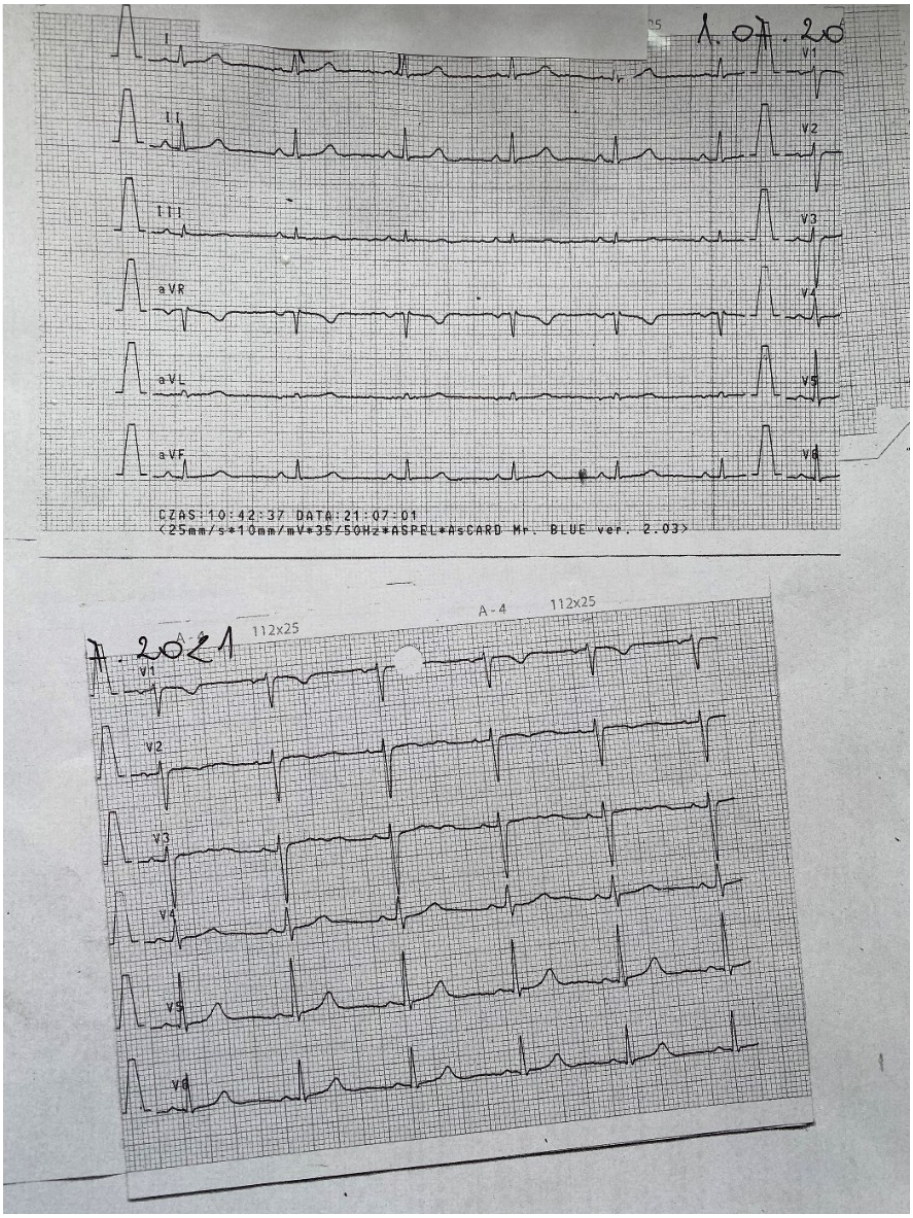

Figure 1. 1 July 2021 baseline. EKG: Sinus rhythm, regular 65/min. The intermediate axis of the heart. The interval P-R: 0.13 [ms] QT,c-0.40 [ms]. In V2-V3, shallow two-phase T waves (standard variant)

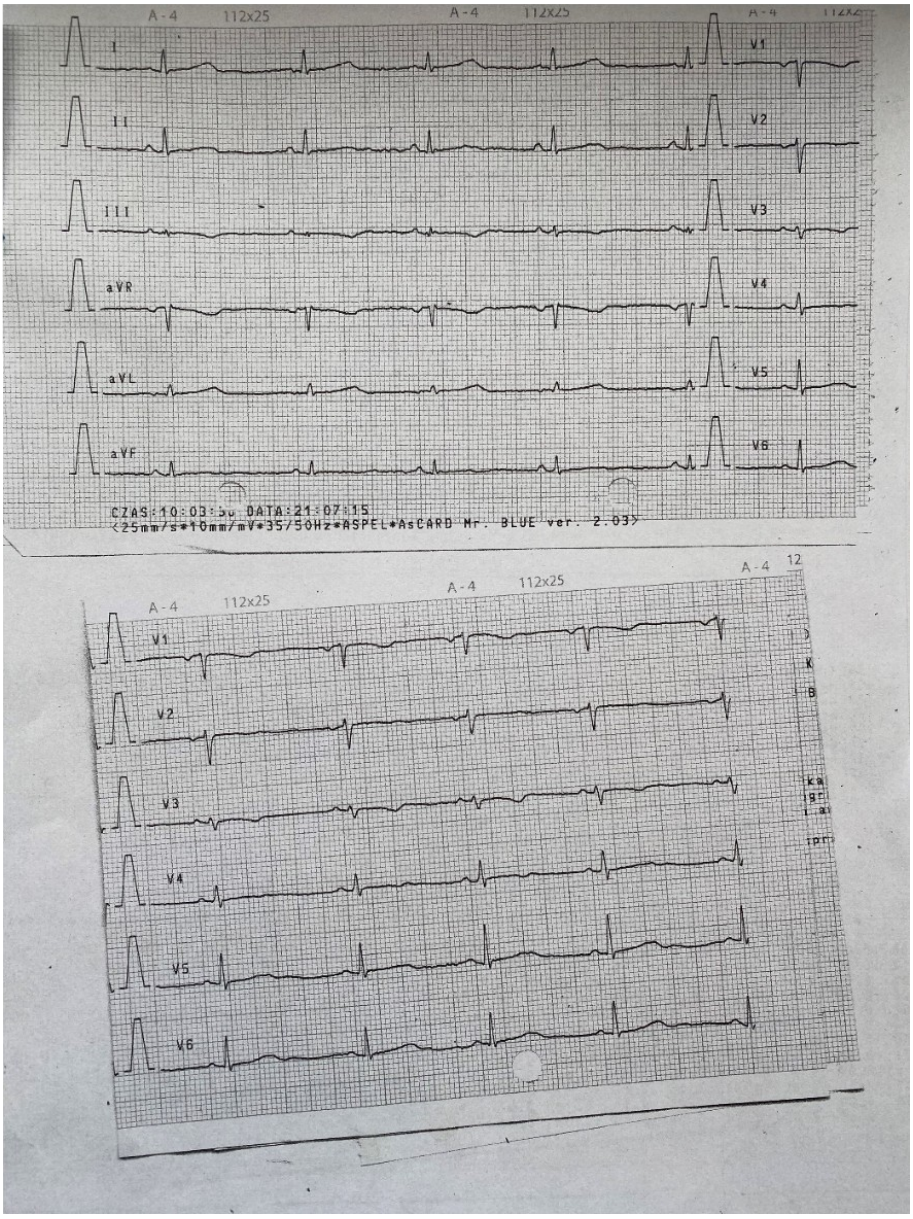

Figure 2. 15 July 2021 during the treatment. EKG: Sinus bradycardia 54/min. Intermediate heart axis. The interval P-R: 0.13 [ms], QTc- 0.52 [ms], flat T in V2, shallow negative T in V3, flat T in V4