1696. Total-deletion mutation of *pncA* as a new mechanism of pyrazinamide resistance in *Mycobacterium tuberculosis* - The first report from Japan

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Background. Pyrazinamide (PZA) is an indispensable first-line anti-tuberculosis drug that is part of the currently used short-course, combination chemotherapy against tuberculosis (TB). PZA is a prodrug that has to be converted to the active form, pyrazinoic acid, by pyrazinamidase (PZase) activity, encoded by the *pncA* gene of *Mycobacterium tuberculosis*, and loss of PZase activity is associated with PZA resistance. Thus most of PZA-resistant strains are due to mutations of the *pncA* gene. Though many *pncA* mutations are known, total-deletion of the gene has never been reported in clinical case yet. We report the first case of PZA-monoresistant TB by total-deletion of the *pncA* gene.

Methods. A 73-year-old man had no history of TB treatment. His chest CT demonstrated multiple discrete nodules in the bilateral upper lung fields and cavitary lesions in right upper lobe.

Results. Sputum examination showed positivity of smear-microscopy, culture and TB-PCR. Together with chronic occupational exposure to silica dust, he was diagnosed of silicotuberculosis. In vitro anti-tuberculosis drug susceptibility testing by standardized proportion method revealed that the isolate was susceptible to isoniazid (INH), rifampin (RIF), rifabutin (RBT), ethambutol (EMB), streptomycin (STR) and levofloxacin (LVFX), whereas it was resistant to PZA. PZA susceptibility testing was carried out in liquid media (Kyokuto Pharmaceutical Industrial Co., Ltd.). Further investigation by the Research Institute of Tuberculosis revealed that the species was identified as *Mycobacterium tuberculosis* sensu stricto and kept no pyrazinamidase activity. Further sequencing analysis revealed the large deletion (22,934bp) including the total *pncA* gene.

Conclusion. Yee DP et al. reported that patients with PZA-monoresistant TB had significantly worse clinical outcomes than patients with fully susceptible strains. PZA resistances were almost due to point mutations in *pncA*. The total-deletion mutation of *pncA* shown in the present case was also highly resistant to PZA. To the best of our knowledge, this is the first reported case of total *pncA* deletion with PZA resistance. Not only *pncA* mutation but also *pncA* deletion will cause PZA resistance.

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