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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1. Number of third-generation cephalosporin-susceptible and resistant pneumococcal meningitis cases. Susceptible: third-generation cephalosporin-susceptible; resistant: third-generation cephalosporin-resistant; PCV7 was introduced in 2010, and PCV13 was introduced 2013. The patients have been decreasing since introduction of vaccination.

Table S1. Characteristics of patients infected with third-generation cephalosporin-susceptible and third-generation cephalosporin-resistant pneumococcal isolates.

False-positive results in SARS-CoV-2 antigen test with rhinovirus-A infection

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Key words coronavirus disease 2019, enterovirus, human rhinovirus, rapid antigen test, severe acute respiratory coronavirus 2.

Since the outbreak of coronavirus disease-2019 (COVID-19) in December 2019, more than 40 million people have been infected and more than 1 million have died. In Japan, approximately 80 000 people have been infected.¹ The gold standard for testing is the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA through reverse transcriptase polymerase chain reaction (RT-PCR).² However, only a few facilities perform RT-PCR testing, while others alternatively perform the antigen test. Espline SARS-CoV-2 (Fujirebio, Tokyo, Japan) is a SARS-CoV-2 antigen detection test in which the nasopharyngeal swab is obtained and tested by immunochromatography based on enzyme immune response.² According to the clinical guidelines in Japan, patients with positive rapid antigen results are declared COVID-19 positive.² The rapid antigen test was introduced for the benefit of obtaining results easily and quickly. We performed multiplex PCR using a FilmArray

Respiratory Panel 2.1 (FilmArray; Bio Mériex, Marcy-l'Etoile, France) for the patients who tested positive through the rapid antigen test. FilmArray Respiratory Panel 2 demonstrated a positive agreement of 91.7% and a negative agreement of 93.8% based on FilmArray Respiratory Panel or two PCR assays targeting *IS1001* for *Bordetella parapertussis*, followed by bidirectional sequencing.³ FilmArray can detect 21 microorganisms simultaneously, including the SARS-CoV-2. Here we report three cases of human rhinovirus A (HRV-A) infection where the patients presented with false-positive results for SARS-CoV-2 on the rapid antigen test.

Table 1 shows the three cases. Case 1 was a 3-year-old boy with trisomy 13, who was admitted to the hospital because of fever, cough, and hypoxemia. Case 2 was a 2-year-old girl with central hypoventilation syndrome, who presented with fever and rhinorrhea, and convulsions due to hyponatremia. Case 3 was a 17-year-old girl admitted due to hypoxemia, with a history of surgery for congenital heart disease. None of these patients came in contact with COVID-19 patients. We determined their SARS-CoV-2 on rapid antigen test results to be positive for SARS-CoV-2 because both the reference lines and test lines appeared within 30 min after testing at admission. However, FilmArray detected HRV/enterovirus and not

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Table 1 Three cases with false-positive results in SARS-CoV-2 rapid antigen tests

	Case 1; 3-year-old boy	Case 2; 2-year-old girl	Case 3; 17-year-old girl
Diagnosis	Acute bronchiolitis	Hyponatremia	Acute pneumoniae
Symptoms	Fever, cough, hypoxemia	Fever, nasal discharge, convulsion	Sore throat, cough, hypoxemia
Underlying diseases	Trisomy 13, very-low birthweight infant, laryngomalacia, post tracheostomy	Central hypoventilation syndrome, central diabetes insipidus, post tracheostomy	Congenital cardiac disease (corrected transposition of great arteries, atrioventricular septal defect)
A history of close contact with COVID-19 patients	None	None	None
Inspection day			
Espline SARS-CoV-2	Day 6	Day 8	Day 2
FilmArray Respiratory Panel 2.1	Day 7	Day 9	Day 2
Production lot number of Espline SARS-CoV-2	K4B-039	K4B-039	K4B-019, K4B-039
Results of FilmArray Respiratory Panel 2.1	Human rhinovirus/enterovirus	Human rhinovirus/enterovirus	Human rhinovirus/enterovirus
Type of enterovirus	Human rhinovirus A85	Human rhinovirus A82	Human rhinovirus A11

SARS-CoV-2. We extracted viral RNA from nasopharyngeal swabs and performed RT-PCR and DNA sequencing to identify the type of enterovirus. In all three cases, we detected HRV-A, not SARS-CoV-2.

From our cases, we have two clinically important suggestions. First, since false positives have a large impact, patients should be selected not only for symptoms but also for a history of close contact with COVID-19 patients, especially in children. A systematic review of 7,780 pediatric COVID-19 patients reported that 19.3% were asymptomatic.⁴ Even in symptomatic patients, there were many nonspecific symptoms such as fever (59.1%) and cough (55.9%).⁴ In addition, 5.6% of the cases were co-infected with other viral infections.⁴ In this systematic review, 75.6% of patients were exposed to the infection from the family.⁴ A history of contact with COVID-19 patients affects the pretest probability more than clinical symptoms only when the risk of social exposure is low. False positives have a large impact on the patient in terms of physical, mental, and financial burden because persons diagnosed with COVID-19 in Japan must be hospitalized.²

Second, we should reconfirm through the RT-PCR test when Espline SARS-CoV-2 is positive at the current epidemic level in Japan. In Japan, even if the rapid antigen test result for symptomatic patients is positive, the causative organism could be more common viruses, including HRV, and the rapid test result could be false positive. No false-positive results for Espline SARS-CoV-2 have been reported owing to cross-reactivity with HRV. In other countries, cross-reactivity between SARS-CoV-2 antigens and other infectious diseases such as other coronaviruses, influenza virus, and *Mycoplasma pneumoniae* has been reported.⁵ The possible reasons for false-positive results could be low prevalence of the disease in Japan and influence of the test kit. The lower the prevalence is the higher the false positive rate of the test becomes. However, Kobe city has a large number of COVID-19 patients in Japan. Additionally, since the three patients were tested with a kit of

the same production lot number (K4B-039), false-positive results may be possible. However, when re-examined using a kit with a different production lot number (K4B-019), the result was again positive in Case 3.

Thus, the indications for rapid antigen tests should be reconsidered, especially in children without any history of the contact with COVID-19 patients. Reconfirmation is warranted through the RT-PCR test when Espline SARS-CoV-2 is positive at the current epidemic level in Japan.

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Disclosure

The authors declare no conflicts of interest.

Author contributions

S.O. wrote the manuscript; A.M. and M.K. provided conceptual advice; S.M., A.M., and T.I. provided technical support, and collected and analyzed data. All authors have read and approved the final manuscript.


Informed consent

We obtained informed consent from the patients' parents to publish this case report.

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A case of “asymmetrical” Graves' disease with lateral radioisotope uptake

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An 11-year-old female presented with thyrotoxicosis and no remarkable medical history, although her mother had Hashimoto thyroiditis. She had experienced dizziness and palpitations for 1 year. Her height and weight were 148 cm (−0.4 SD) and 38 kg (body mass index SDS −0.16 SD), respectively, and reported no height spurt or weight loss. She displayed tachycardia and no tremor nor proptosis. Her goiter was elastic, soft, almost equally swollen on both sides by visual inspection and was grade 1 by the World Health Organization classification. No palpable thyroid nodules were noted.

Figure 1a displays the clinical course chart. Her initial thyroid-stimulating hormone and free thyroxine levels were <0.1 μU/mL and 3.3 ng/dL, respectively, and her thyroglobulin antibody, thyroid peroxidase antibody, thyrotropin receptor antibody (TRAb), and thyroid-stimulating antibody (TSAb) levels were 600 U/mL, 258 U/mL, <1.5 U/L, and 132%, respectively. The thyroid ultrasound displayed a right lobe of 5.9 mL and a left lobe of 7.7 mL (standard <6.1 mL and <4.9 mL, respectively) (Fig. 1b). Both lobes displayed a coarse texture and increased echogenicity, and there were no findings of increased vascularity or thyroid nodule. ¹²³I thyroid scintigraphy was performed, because of the low TRAb

levels. Increased iodine uptake was observed, predominantly in the left lobe in color scintigraphy, but increased uptake in the right lobe was also noted in a monochrome image. The total iodine uptake was 75%. We further recalculated the iodine uptake in both lobes separately and identified uptakes of 56.6% in the left lobe and 20.7% in the right lobe (Fig. 1c). From these results, we diagnosed her with Graves' disease and initiated methimazole (MMI). We added potassium iodide (KI) because the effect of treatment with MMI alone was insufficient. However, she felt leg pain and her the creatinine kinase level was 88 IU/L. Thus, we stopped MMI and the leg pain improved. With KI therapy, the hyperthyroidism was almost controlled. In general, juvenile Graves' disease has a high recurrence rate. Furthermore, MMI cannot be used for any future recurrence in this patient because of its side effects. Therefore, total thyroidectomy was performed 4 months after the first medical examination. Medium-sized follicles and collagen fibers were distributed throughout the pathological specimen and no nodules were present. Lymphoplasmacytic infiltration with germinal centers was also observed around the remaining follicles that matched lymphoplasmacytic thyroiditis (Fig. 1d). These findings were found in both lobes equally. Finally, we concluded that she had “asymmetrical” Graves' disease. She is currently taking levothyroxine and keep euthyroid. Informed consent was obtained from her parents for publication of this report.

This case did not present as silent thyroiditis because of her long clinical course and increased iodine uptake. Autonomously functioning thyroid nodule (AFTN), Marine-Lenhart

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