

ARDS, Influenza, and a negative rapid influenza screen

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The influenza pandemic was a known threat but of unknown severity during the fall of 2009. There was widespread use of rapid influenza diagnostic tests (RIDT) during this time even though emerging reports showed that the sensitivity of this test was widely variable depending on manufacturer and prevalence of influenza in the community. In this case series, we report on 3 young Hispanic males with severe H1N1 infection, but with negative rapid influenza tests. It demonstrated a failure of rapid influenza testing to diagnose serious cases. Here these cases will be described and the role of influenza diagnostic modalities will be discussed.

Starting in March 2009 in La Gloria, Mexico the first cases of novel influenza A H1N1 virus began to appear at a rapid pace.¹ Besides the alarming number of cases that began to spread throughout the world, another great concern dealt with the population affected. This virus was affecting the young at a higher rate and with greater severity than the traditional influenza virus.² Treatment of severe cases of influenza depended on initiating antiviral medication as soon as possible to reduce the severity and duration of illness. To assist in improving the time to diagnosis, several companies had already developed a rapid influenza diagnostic test. These were in widespread use by medical facilities throughout the world, but untested to this novel virus. Much was unknown in the fall of 2009 when from October 17 to October 21st our hospital admitted

3 young Hispanic males with similar presentations of severe respiratory distress and bilateral infiltrates. These patients did not know or have contact with each other prior to admission.

Case 1

A 32yo Hispanic male with no past medical history presented with 1 week of fever, chills, diarrhea and productive cough. On initial presentation he had a temperature of 104 with labored respirations. Chest radiograph (**Figure 1**) showed bilateral infiltrates. Physical exam showed a young male in moderate respiratory distress with crackles in all lung fields. Arterial blood gas (ABG) revealed PaO₂ of 66mmHg on FiO₂ 100% nonrebreather mask. Otherwise he had mildly elevated transaminases. Rapid influenza screen was negative. CT scan (**Figure 2**) revealed extensive bilateral consolidations. He did not improve with a short trial of BiPAP and was intubated. Antibiotics were started in the emergency department.

Oxygenation continued to be difficult and he required bi-level ventilation with paralysis and prone positioning to keep his PaO₂ above 70mmHg. He experienced multisystem organ failure with extensive vasopressor use and attempts of dialysis when his blood pressure allowed. Ultimately he died after 14 days. Testing for H1N1 via nasopharyngeal swab was positive via RT-PCR and all other cultures were negative.

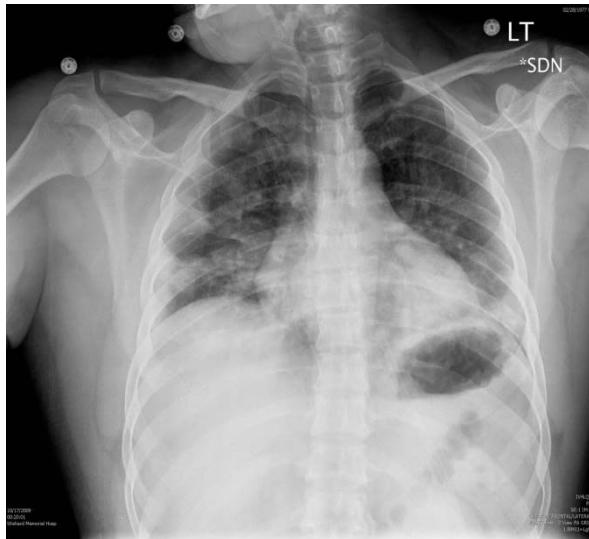


Figure 1 – PA chest of patient 1

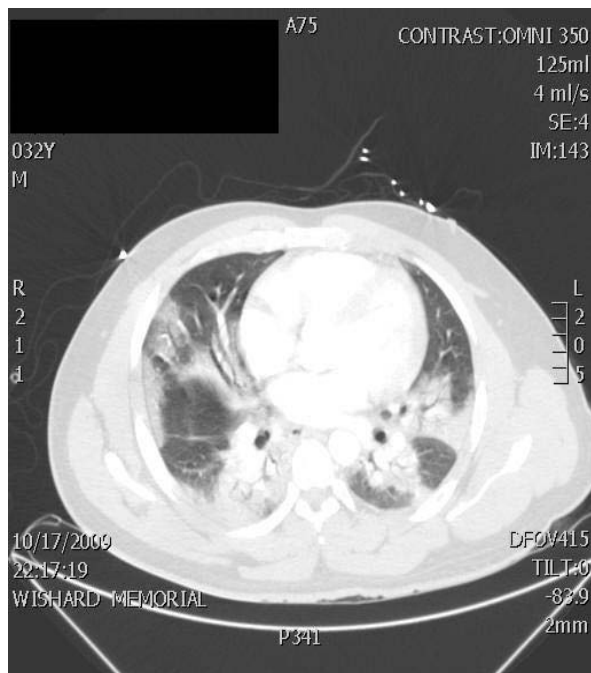


Figure 2 – Axial chest CT of patient 1

Case 2

A 47yo Hispanic male with a history of GERD presented with 1 week of cough, fever, nausea/vomiting and mild dyspnea. Chest radiograph showed diffuse bilateral infiltrates (Figure 3). CT scan of the chest (Figure 4)

confirmed these extensive infiltrates as well as ground glass opacities. His ABG revealed mild hypoxemia on room air. Rapid influenza screen was negative. Broad spectrum antibiotics were begun.

Bronchoscopy was performed early on in his hospitalization. Prior to this procedure he was electively intubated due to progression of his hypoxia and infiltrates. He required several days of mechanical ventilation but did respond slowly to treatment. He was successfully extubated on day 6. HIV, legionella, fungal immunoassays, and PPD were negative. All cultures, including BAL, were negative. Influenza RT-PCR of nasopharyngeal and BAL samples were also negative. Due to the clinical presentation and lack of positive cultures, this case was assumed to be associated with influenza.

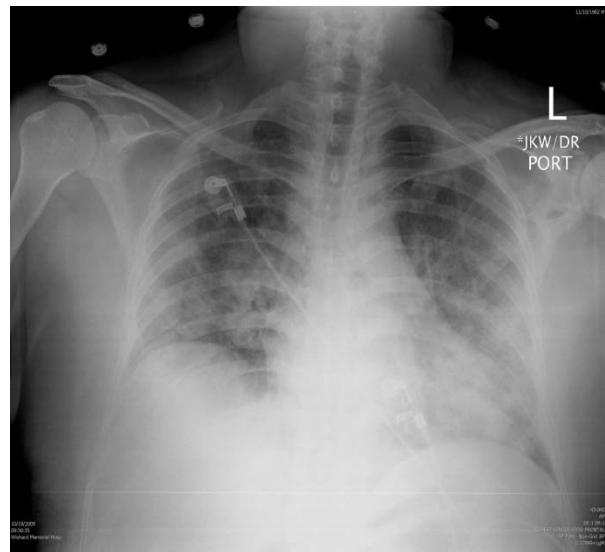


Figure 3 - PA chest of patient 2

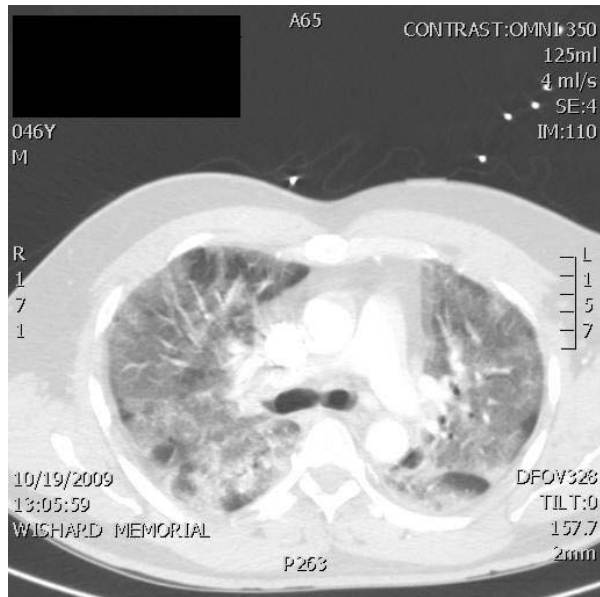


Figure 4 – Axial chest CT of patient 2

nasopharyngeal swab Influenza RT-PCR came back positive. All other cultures were negative.

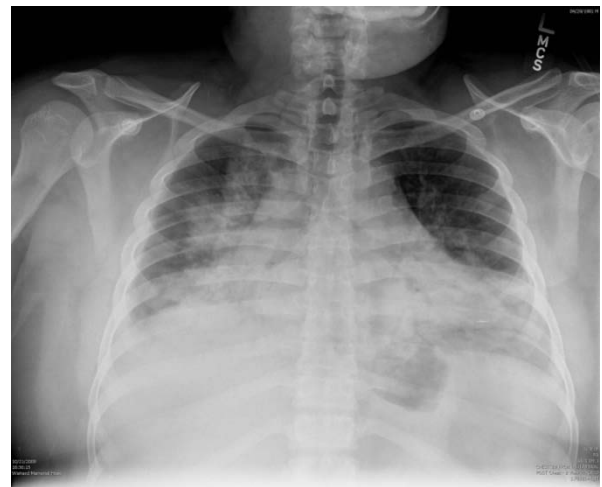


Figure 5 - PA chest of patient 3

Case 3

A 28yo Hispanic male with no past medical history presented with cough, fever, SOB, diarrhea, nausea and vomiting that began eight days prior to admission. Physical exam revealed basilar crackles. Lab analysis showed a PaO₂ of 66mmHg on FiO₂ 100% nonrebreather mask, potassium of 3.6 mEq/L, a CK of 742 u/L and a troponin of 0.74. Rapid influenza was negative. Chest radiograph showed bilateral infiltrates (**Figure 5**). CT of the chest (**Figure 6**) confirmed extensive bilateral consolidations with air bronchograms. Broad spectrum antibiotics were begun.

He also underwent bronchoscopy with elective intubation. He continued to be severely hypoxic so bi-level ventilation and prone positioning were employed, without improvement. He was changed to high frequency oscillatory ventilation with gradual improvement in oxygenation. However he still experienced multisystem organ failure and needed extensive vasopressor use to maintain an adequate blood pressure. He rapidly decompensated and passed away on day 10. His

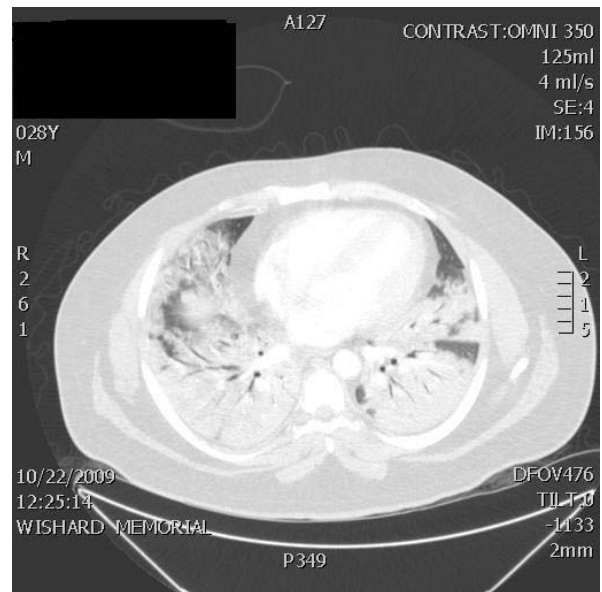


Figure 6 – Axial chest CT of patient 3

Discussion

Management of severe influenza pneumonia is difficult in all age groups. Early intervention and treatment is key with death as a real concern. The utility of the rapid influenza screen has come into question over the past few years as the sensitivity has been shown to be low and variable.³ This variability appears to be even

wider with the 2009 pandemic Influenza A (H1N1) virus.

Rapid influenza testing can yield positive results in 30 minutes or less and can distinguish between A and B types. However, it cannot distinguish between subtypes (ie. H1N1 strain) and results are affected by many variables – site and quality of specimen (nasal vs nasopharyngeal), time of illness onset, age of patient, time of collection to testing and storage.

From April to May of 2009 the Naval Health Research Center found the sensitivity of rapid influenza testing to be 51%⁴. This is high compared to later studies in both the United States and abroad. US data found sensitivities ranging from 10% to 47% for various RIDT's.^{5,6} An Australian study placed the number at 25% during their main influenza season⁷ and a German study revealed only 16 of 144 (11%) confirmed cases of influenza were positive with the rapid screen.⁸

Data from previous years held similar variability and poor sensitivity. Two examples of this are the Quidel QuickVue Influenza A+B and BinaxNOW Influenza A&B Rapid test. The Quidel test showed a sensitivity of 27% for the 2007-8 influenza season.³ The BinaxNOW test showed a sensitivity of 37.5% for the 2007-8 season and 51.9% for the 2008-9 season.⁸

Due to the high possibility of a false negative, confirmation of negative cases should be verified with either a viral culture or RT-PCR. The RT-PCR has been shown to be 86-100% sensitive and are the comparison for many studies on RIDT's.⁹ Viral cultures remain the gold standard (**Chart 1**).

It is encouraging that specificity has remained high with the RIDT's and a positive result will allow proper treatment sooner than RT-PCR or a viral culture. However a negative rapid influenza test should be viewed with speculation. If suspicion for influenza is high it is better to treat as if they are positive until a confirmatory test has been received.

Influenza diagnostic test	Method	Availability	Typical processing time	Sensitivity for 2009 H1N1 influenza	Distinguishes 2009 H1N1 from other A
Rapid influenza diagnostic test	Antigen detection	Wide	0.5 hour	10-70%	No
Direct & indirect immunofluorescence assays	Antigen detection	Wide	2-4 hours	47-93%	No
Viral isolation in tissue culture	Virus isolation	Limited	2-10 days	-	Yes
Nucleic acid amplification test	RNA detection	Limited	48-96 hours	86-100%	Yes

Chart 1 – Comparison of influenza diagnostic tests

References

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