Posterior Pharyngeal Wall Follicles as Early Diagnostic Marker for Seasonal and Novel Influenza

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**Background:** Rapid and accurate diagnosis is essential for containing the novel influenza A/H1N1 pandemic. Polymerase chain reaction (PCR) testing is an accurate diagnostic method, but it is not routinely available worldwide. We herein evaluated the usefulness of pharyngeal “influenza follicles” in diagnosing seasonal influenza and influenza A/2009 (H1N1) pdm.

**Methods:** Between August 3 and October 29, 2009, we evaluated 87 patients with influenza-like symptoms. Twenty-three had influenza follicles (22 on initial evaluation; 1 on follow-up) while 64 did not. Considering these two groups, we then compared the positive cases using rapid diagnostic testing (confirmed by PCR). In addition, 419 cases of seasonal influenza diagnosed between 2003 and 2009 were examined for the presence of influenza follicles based on Miyamoto’s 2007 definition, and new exclusion criteria were developed.

**Results:** Among the 23 patients with influenza follicles, 21 were diagnosed with novel influenza. Of these, follicles were present on initial evaluation in 20 and on follow-up in 1. None of the 64 patients without influenza follicles were diagnosed with influenza (sensitivity 100%, specificity 97%). Among the 419 patients diagnosed with seasonal influenza between 2003 and 2009, influenza follicles occurred in all type A/H3N2, A/H1N1, and B cases (sensitivity 95.46%, specificity 98.42%). Thus, follicles were considered a specific sign of influenza.

**Conclusion:** Influenza follicles occur in both seasonal and novel influenza. This identification method has higher diagnostic sensitivity and specificity than rapid diagnostic testing and is a promising clinical tool for diagnosing influenza when PCR is unavailable, or in pandemic situations.

**Key Words:** influenza, influenza follicle, seasonal influenza, novel influenza, early diagnostic marker, posterior pharyngeal wall follicle

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INTRODUCTION

Concerns over influenza pandemics have been realized with human-to-human transmission of the novel influenza A/2009 (H1N1)pdm. The first cases were identified in April 2009, and the epidemic largely subsided by March 2010. However, from December 2010 to the present, there has been a resurgence of cases, and as of April 2011, infection was spreading in western Japan.

To contain influenza pandemics, an important preventive measure is rapid and accurate diagnosis in conjunction with the exclusion of febrile non-influenza illness. Polymerase chain reaction (PCR) testing is an accurate diagnostic method but is not routinely available.

Influenza rapid diagnostic tests, which use pharyngeal swab samples, are available as an alternative to PCR, but these are not particularly sensitive and are not entirely useful for identifying the cause of disease because negative results do not necessarily exclude influenza infection. Reports from the United States estimate that the sensitivity of these kits for novel influenza A/2009 (H1N1)pdm is 40 to 69%. In Japan, a survey conducted in Kobe and Osaka in May 2009 estimated that sensitivity ranged from 53.5 to 77%. Both are lower than the sensitivity of rapid diagnostic kits for seasonal influenza (80 to 90%).

On September 18, 2009, the Japanese Ministry of Health, Labor, and Welfare (JMHLW) issued unprecedented guidelines regarding the diagnosis and treatment of novel influenza. These included: (1) if a physician decides, based on clinical findings and regional epidemiologic patterns of infection, to start anti-influenza viral therapy, rapid diagnostic or PCR testing is not necessary; and, (2) for treatment reimbursement, when starting anti-influenza viral therapy, rapid diagnostic testing is not necessary. Previously in Japan the clinical diagnostic criteria for reporting influenza to the MHLW were stricter in terms of clinical requirements and often required pathogenic or serologic testing.

PCR is considered the diagnostic gold standard, but during large outbreaks of novel influenza, systems are rapidly shut down because of cost and laboratory staff constraints, except under special circumstances. For example, PCR testing was performed only on the first novel influenza case in Japan on May 18, in mid-July during the cluster outbreak, and at fixed-point observations in medical institutions. In addition, shortages of rapid diagnostic kits arose in many areas in Japan during this period. In many countries and regions of the world, PCR and rapid diagnostic tests are not available in sufficient supply.

Modern medicine may overemphasize the use of advanced equipment and technology, such as electron microscopy and PCR, when diagnosing viral diseases, including influenza. Assessment of patient history and physical examination remain the basis of clinical medicine, and in the face of an influenza pandemic access to new technologies, such as PCR and influenza antigen rapid diagnostic tests, may be limited, forcing physicians to go back to the basics.

Influenza, except when complications occur, has no specific clinical (pathognomonic) findings. We explored whether, as with Koplik’s spots in measles, a specific clinical finding could be identified and used to diagnose disease in patients.

We previously reported the findings of a prospective study on pharyngeal “influenza follicles” observed in cases with seasonal influenza A/H3N2 treated between 2003 and 2004. As this finding was highly sensitive and specific for diagnosis, the presence of these follicles has been recorded in medical records since 2004.

After the first case of novel influenza A/H1N1 was confirmed in Japan, we examined patients with influenza-like symptoms for the presence of influenza follicles and determined the diagnostic utility of this finding for novel influenza. We also retrospectively analyzed seasonal influenza case records and clinical photos from as many cases as possible over the past 7 years to confirm the clinical definition of influenza follicles.

We herein present results based on clinical evidence, of seasonal influenza as well as novel influenza A/H1N1pdm, that indicate that influenza follicles appear early in disease progression when rapid diagnostic tests are negative. This visual method is a promising clinical tool for diagnosing influenza.
METHODS

Patients
This study was approved by the institutional review board at Tsukuba University Hospital, Mito Medical Center. Written (2003-2004, seasonal; 2009, A/H1N1pdm), or verbal (2005-2009, seasonal) informed consent was obtained from all participants before enrollment.

Novel influenza. On May 16, 2009, the first case of novel influenza in Japan was confirmed. Between August 3 and October 29, 2009, we performed rapid diagnostic tests on 87 patients with upper respiratory infection symptoms and fever (in positive patients, PCR was performed to confirm novel influenza A/H1N1).

We confirmed our first patient with novel influenza on August 16. After a rapid diagnostic test positive for type A, novel influenza A/H1N1 was confirmed by PCR at the public health department. From the first case of novel influenza at our clinic on August 16, till October 29, the Ibaraki Prefectural Institute of Public Health reported no cases of seasonal influenza in its infectious disease surveillance. That is, all patients with type A influenza on rapid diagnostic test were diagnosed as having novel influenza.

We divided patients into the following groups: I - A, influenza follicles on initial evaluation; I - B, influenza follicles on follow-up evaluation and diagnosis of type A influenza on rapid diagnostic testing; and, II, no influenza follicles on initial evaluation and negative for type A influenza on rapid testing.

For influenza antigen detection, we used an influenza antigen rapid diagnostic kit (BD Flu Examen, Nippon Becton, Dickinson and Co.) with nasal swab samples.

All patients were followed until recovery; they were examined by two clinicians (AM and SW) a maximum of four times over a period of up to 6 days at our clinic.

Inter-observer reliability was demonstrated using 72 cases from 2003 to 2009 that were independently examined by two observers (A and B) for the presence or absence of influenza follicles, followed by clinical laboratory diagnosis of influenza (rapid diagnostic tests and/or PCR tests). The agreement beyond chance statistic, $\kappa$, was calculated.

Seasonal influenza. After publication of the original article by Miyamoto in 2007,9 we conducted a retrospective review of influenza cases during the previous 7 years (2003-2009). Over that period, a total of 68,216 patients visited our clinic, including 25,244 during the October to March periods, 1694 who presented with fever plus either cough or sore throat, and 847 with rapid temperature rise within the first 24 hours of illness. These 847 patients were examined for the presence or absence of influenza follicles, and underwent laboratory examination by rapid diagnostic test and diagnostic antibody titers (hemagglutination inhibition).

During the winter of 2003-2004, all 53 of the A/H3N2 patients had influenza follicles on initial examination. We encountered 103 influenza patients in 2004-2005 (type A, 23; type B, 80); 40 in 2005-2006 (type A, 36; type B, 4); 40 in 2006-2007 (type A, 16; type B, 24); 44 in 2007-2008 (type A, 33; type B, 11); and, 139 in 2008-2009 (type A, 37; type B, 102).

Of the 419 patients that we diagnosed with influenza between 2003 and 2009, 166 had type A and 200 had type B, and influenza follicles were present in all cases of type A/H1N1 and cases of A/H3N2 (Figure 1A). In type B influenza, these follicles were present in 199 of 200 patients on initial evaluation, and in the remaining case on day 2 (Figure 1B). From these 419 cases, we confirmed the diagnostic criteria and set new exclusion criteria for influenza follicles.

Statistical analysis
Values are shown as mean ± SD and median. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated to evaluate the diagnostic accuracy of the presence of influenza follicles as a sign of novel influenza (AM and WS analyzed the data). Inter-observer reliability was assessed using the kappa ($\kappa$) statistic with significance level $p<0.001$ with SPSS (ver.18) software.

RESULTS

Novel influenza
Among the 87 patients encountered during the early stages of the epidemic, 22 were in group I - A, 1
was in group 1-B, and 64 were in group II. Among the 23 patients in group I (A and B), 4 were male and 19 were female. The mean age was 15±6.7 years (range, 7 to 39 years; median, 14 years). Mean duration from symptom onset to evaluation was 7.8±5.3 h (range, 3 to 20 h; median, 5 h). Mean maximum temperature until evaluation was 38.6±0.7℃ (range, 37 to 39.6℃; median, 38.9℃).

Among 4 patients in group I who were followed up because they had influenza follicles on initial evaluation despite negative results for type A on influenza rapid testing, 3 were determined to be type A-positive upon diagnostic testing in day 2, and 1 was found to be type A-positive in day 3.

Regarding the 1 patient in group I-B, who had no influenza follicles on initial evaluation but who was later diagnosed with type A, the follicles appeared on day 6 after initial evaluation, and rapid diagnostic testing at that time was positive for type A influenza.

Among 64 patients in group II without influenza follicles, none were positive for type A on rapid testing. Among the 64 patients in group II, 29 were male and 35 were female. Mean age was 18.7±14.8 years (range, 3 to 47 years; median, 14 years). Mean duration from symptom onset to evaluation was 13.9±5.8 h (range, 3 to 33 h; median, 13 h). Mean maximum temperature until evaluation was 38.3±0.5℃ (range, 37.5 to 40.1℃; median, 38.2℃).

Hence, of the limited cases available, 23 patients showed influenza follicles, among whom 21 were diagnosed with novel influenza. The frequency of influenza follicles on initial evaluation was 20/21 (95.2%) (in 1 patient in group I-B, influenza follicles appeared on day 6; the patient became type A positive on the same day). The specificity was therefore 21/23 (91.3%).

Of special note is that among the 20 type A influenza patients with influenza follicles on initial evaluation, rapid diagnostic testing on initial evaluation was positive in 16 (80%). In contrast, the frequency of influenza follicles at initial evaluation was 20/21 (95.2%). Thus, the number of cases missed as “rapid test negative” was greatly reduced.

Therefore, in the diagnosis of type A influenza among patients positive for type A influenza on rapid testing, all had influenza follicles, giving a sensitivity of 100%. In addition, when no influenza follicles were present during the clinical course, the specificity for ruling out influenza was 97%. Positive predictive value was 91% and negative predictive value was 100%.

### Diagnostic criteria for influenza follicles

From the 419 cases of seasonal influenza from 2003-2009, we confirmed the diagnostic criteria and set new exclusion criteria for influenza follicles.

Influenza follicles are small, isolated lymph follicles (diameter, 2-4 mm) that appear on the posterior wall of the pharynx during early influenza infection. Many are hemispheric and have a well-circumscribed base but no constriction. These are classified on the Yamada/Fukutomi (Y/F type) classification, a classification widely used in Japan that is based on the morphology of gastric polypoid lesions, as Y/F type II lesions.

However, in the present cases, lesions more like Y/F type I, which are not well circumscribed, were not uncommon. The surface of the follicles had a characteristic tense, shiny, and translucent appearance. They were magenta and resembled small salmon roe. On the second day, the surface tension of the follicles disappeared, their luster was lost, and there was slight atrophy and loss of translucency. The follicles were raised, but became less distinct, and began to resemble Y/F type I lesions. On the third day, the follicles, which had a tense raised appearance on day 1, had a broader base and slightly larger diameter. They were cloudier and had lost their magenta appearance. Early-stage follicles were typically round or hemispheric, but rice grain- or teardrop-shaped lesions were also seen, and adjacent follicles sometimes coalesced. Figures 2B-F show follicle variants.

Figures 1C and 1D show typical pharyngeal findings for one patient. This patient had influenza follicles on initial evaluation (Figure 1C) and was negative for type A influenza on rapid testing performed that day but became positive on day 3 (Figure 1D). We examined this patient for 3 consecutive days. Figures 1E and 1F show findings in non-influenza febrile illness.
According to the usual diagnostic procedure, the tongue, tonsils and palatopharyngeal arch areas of the oropharynx are examined in patients with common cold or influenza. Even if the posterior pharyngeal wall is inspected, the presence or absence of erythema is noted, but attention is not focused on elevated lesions like follicles. It is important to thoroughly inspect all areas of the posterior pharyngeal wall in order to identify influenza follicles. Reflectiveness is the primary characteristic of follicles; they are more reflective than the surrounding tissue. Figure 3A–E shows the appearance of follicles under various lighting conditions. For best results, a single-light LED should be used to illuminate the oral cavity (Figure 3B).

**Exclusion criteria for influenza follicles**

In upper respiratory tract infections, isolated lymph follicles of the pharynx are common. The following features of pharyngeal lymph follicles distinguish them from influenza follicles. Follicles that are already cloudy early on in influenza infection are not influenza follicles. Moreover, follicles that resemble Y/F type I lesions during early infection are unlikely to be influenza follicles, as are polymorphic follicles (Figure 1E–F). To avoid overdiagnosis, the most important point is that even if the morphology of the follicles suggests influenza, cases with lesions that are not obviously redder than the surrounding posterior pharyngeal wall mucosa should be judged to not have influenza.

**Morphological classification of influenza follicles**

Using a system of inclusion and exclusion criteria, we made the following morphological classification of influenza follicles.

1) **Definitive influenza follicles**

Round and hemispheric follicles appearing on the posterior wall of pharyngeal mucosa that are isolated from each other with a well-defined border are classified as Y/F type II. Follicles with well-defined and constricted borders like rice grain- or teardrop-shaped lesions are also discriminative. The follicles are small (diameter, 1–2 mm) and all are nearly identical in size in a given patient. The follicles are magenta in color and resemble small salmon roe with a surface that has a characteristic tense, shiny, and translucent appearance. These characteristic follicles are observed almost exclusively in influenza infection, especially in the early stage of infection (Figure 4A–B).

2) **Probable influenza follicles**

Follicles classified as Y/F type I are elongated rather than perfectly symmetrical. They are translucent in appearance and persist for about 3 days. They are redder in color than the surrounding pharyngeal mucosa. Adjacent follicles sometimes coalesce. These follicles are observed at the middle stages of influenza infection (several days after onset) and are almost always specific to influenza infection (Figure 4C–D).

3) **Non-specific follicles**

Adjacent, isolated lymph follicles often coalesce with each other and become larger in size with polymorphic shapes, meaning that follicles of various sizes are seen on the pharyngeal mucosa. The Y/F type changes from type II to I (Y/F type II are newly established follicles with a well-circumscribed shape and a clear outline; these change to Y/F type I). Follicles lack well-defined and constrictive borders, and are whitish red in color with a progressive change in color from magenta to white. These follicles can be seen in rather late stages of influenza infection; however, they are not specific to influenza. If only one definitive or probable follicle is seen among many follicles, influenza infection should not be suspected (Figure 4E–F).

**Inter-observer reliability**

In a total of 72 cases collected between 2003 and 2009 that were independently examined by observers A and B for the presence or absence of influenza follicles, observer A and observer B both judged 53 cases as influenza and 9 cases as non-influenza. The remaining 10 cases were judged differently by the two observers. Following rapid diagnostic tests and/or PCR tests, a total of 58 cases were confirmed to have influenza and 14 were confirmed to be non-influenza (Figure 5). The precision of clinical examination of influenza follicles was demonstrated by the statistic of agreement beyond chance, $\kappa = 0.557$ (P<
Figure 1. Influenza follicles (IF) in seasonal A/H1N1 influenza (Panel A) and type B influenza (Panel B). Pharyngeal findings in the same patient on initial evaluation (Panel C) and on day 3 (Panel D). The influenza follicles (IF) are flattened, have a broader base, and are cloudy. Panels E and F show follicles in a febrile disease that is not influenza. The follicles are polymorphic or similar to aggregated small nodules. Even those that are round or rice grain-shaped and resemble influenza follicles are usually not redder than the surrounding pharyngeal mucosa.

Figure 2. Influenza follicles (IF) on the posterior wall of the oropharynx. Typical influenza follicles (Panel A) and variations (Panels B-F).
Figure 3. Comparison of light sources commonly used in clinical settings.
Single light source white LED with wide illumination: the subject was aware of glare (Panel A). Single light source LED with narrow illumination: there is sufficient illumination to inspect the posterior pharyngeal wall (Panel B). LED with 4 lights: there is high illumination, but because of the absence of shading, the solid appearance of the small influenza follicles is missed (Panel C). Bluish LED light: the redder appearance of the influenza follicles in contrast to the surrounding pharyngeal mucosa is missed (Panel D). Conventional older penlight: the redder appearance of the influenza follicles in contrast to the surrounding mucosa is concealed (Panel E).

Figure 4. Morphological classification of influenza follicles.
Of the limited cases examined to date, the incidence of positive identification of influenza follicles in non-influenza febrile disease cases was 1 in 14 (7%) (Observer A). A retrospective review of cases from 2004-2008 revealed the incidence of positive identification of influenza follicles in non-influenza febrile disease cases to be 7% (2004-2005), 6% (2005-2006), 5% (2006-2007), 6% (2007-2008), and 5% (2008-2009).

Pathophysiology of the special features of influenza follicles

Isolated lymph follicles in the posterior pharyngeal wall are part of the Waldyer throat ring.14,15 The lymph follicle is filled with a lymph plasma-rich matrix. Lymph plasma coagulation leads to fibrin deposition, and the fibrin is dissolved as fibrinogen in lymph plasma.16 Thus, the surface of the newly established follicles has a characteristic tense, shiny, and translucent appearance. Within a few days, the surface tension dissipates, the luster is lost, and there is a slight atrophy and loss of translucency.

DISCUSSION

More than 900 studies on the diagnostic performance of clinical signs and symptoms in predicting influenza infection have been published.17 Call et al reviewed 6 major studies including 7105 patients with high-grade levels of evidence (Grade of Evidence A and B).18,19,20,21,22,23 In this review, the sensitivity, specificity, positive likelihood ratio (LR+), negative LR, and diagnostic odds ratio (DOR) were estimated (all with p<0.05) and reported for the clinical test characteristics of fever, feverishness, cough, myalgia, malaise, headache, sore throat, sneezing, nasal congestion, chills, vaccine history, fever and cough, and acute onset.

None of the studies assessed the precision of influenza diagnosis. No single clinical finding consistently had a LR+ high enough to clinically diagnose influenza, nor did any single finding have LR− low enough to clinically rule out influenza.

Thus, of the limited cases available to date, the LR+ of our cases (presence of influenza follicles) was 21/(21 + 0) ÷ 2/(2 + 64) = 33.3. This LR+ is higher than the highest LR+ in the presented review (the clinical usefulness of fever and cough in persons aged 60 years or older (LR+: 5.0)19 (LR− of our cases was 64/(2 + 64) ÷ 0/(2 + 64) = ∞).

PCR is considered the diagnostic gold standard, but during large outbreaks of novel influenza, systems are rapidly shut down due to cost and laboratory staff constraints. In Japan, after the first case of infection was confirmed on May 16, 2009, the number of infected people rapidly increased, and PCR was not performed, except in mid-July for some cluster surveillance. In addition, shortages of rapid diagnostic kits have occurred in many areas in Japan. These rapid diagnostic kits and PCR capacity are also in short supply in many regions of the world. By what standards, then, should novel influenza be diagnosed in these circumstances?

During influenza epidemics, large numbers of patients with influenza symptoms are likely to present over a very short timeframe. In Sapporo, 300 outpatients visited after-hours clinics on a Sunday. It was neither possible nor would it be practical to administer rapid diagnostic tests to all patients. Further, considering that the reported sensitivity of rapid antigen diagnostic tests in novel influenza A/H1N1 is only 40 to 50%, half the cases would have been missed.

Influenza follicles were first reported by Miyamoto in type A/H3N2 influenza,9 and then in type A/H1N1 and type B influenza. In 2009 in Japan, we found that among 21 patients with novel influenza A/H1N1, influenza follicles were present on initial evaluation in 20 (95.2%). Rapid testing was positive in 16 of 20 patients (80%; previous reports range from 40 to 69%1 and 53.5 to 77%2,3). When rapid diagnostic tests were negative, influenza follicles were also useful for
diagnosis. Among patients without influenza follicles, none were diagnosed with influenza. Thus, these follicles appear to be specific for influenza.

Regarding the term "influenza follicles," however, there are in fact no lymph follicles pathophysiological-specific to influenza. Rather, this term refers to the tense, shiny, uniformly-sized, and translucent follicles resembling small salmon roe (which are characteristic of new lymph follicles) that are observed during the initial stage of influenza. These follicles are observed in influenza because it has one of the shortest incubation times (time from antigen exposure to onset) among all infections, with many viruses invading the body simultaneously, resulting in clear manifestation (even to the patient) and a very short time from onset to consultation. Due to the short incubation period and extremely rapid onset of multiple symptoms, patients can often recall the precise time they became ill, and they seek diagnosis at very early stages of infection. The uniformity in timing with which they seek examination means that doctors can observe typical influenza follicles (diameter, 1-2 mm), which are all nearly identical in size in a given patient.

Because these follicles are observed only in influenza infection, influenza follicles are highly specific, and they are clinically very useful for the diagnosis of influenza. With proper training, this finding can be confirmed in 10 seconds. In countries and regions where rapid testing cannot be performed, and in pandemic situations with multiple concurrent cases, such as the situation following the March 11, 2011 Great Eastern Japan Earthquake and ongoing evacuation, detection of influenza follicles could enable convenient and rapid diagnosis of influenza.

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