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ORIGINAL ARTICLE

Are atypical lymphocytes present with viral influenza-like illnesses (ILIs) in hospitalized adults?

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Abstract The purpose of this investigation was to determine if atypical lymphocytes were of diagnostic value in viral influenza-like illnesses (ILIs) in hospitalized adults during the influenza season. Are atypical lymphocytes present with viral ILIs in hospitalized adults? During the influenza season, hospitals are inundated with influenza and viral ILIs, e.g., human parainfluenza virus-3 (HPIV-3). Without specific testing, clinically, it is difficult to differentiate influenza from ILIs, and surrogate influenza markers have been used for this purpose, e.g., relative lymphopenia. The diagnostic significance of atypical lymphocytes with ILIs is not known. We retrospectively reviewed the charts of 35 adults admitted with pneumonia due to viral ILI. The diagnosis of 14 patients was by respiratory virus polymerase chain reaction (PCR). During the 2015 influenza A season with ILIs, atypical lymphocytes were not present in influenza A (H_3N_2) patients but atypical lymphocytes were present in some ILIs, particularly HPIV-3. With viral ILIs, atypical lymphocytes should suggest a non-influenza viral diagnosis.

Introduction

During the influenza season, respiratory viruses cocirculate with influenza and may present as viral influenza-like illnesses (ILIs), human metapneumovirus (hMPV), rhinovirus/enteroviruses (R/E), respiratory syncytial virus (RSV), and human parainfluenza virus-3 (HPIV-3) [1]. An ILI may be defined as a non-influenza viral lower respiratory infection accompanied by fever, chills, and myalgias. While definitive viral diagnosis may be made by respiratory viral polymerase chain reaction (PCR) of nasopharyngeal specimens, clinically, it is difficult to differentiate influenza from viral ILIs in hospitalized adults [2, 3]. Viral PCR is available in many, but not all, hospitals, but it is expensive and all adults admitted with an ILI are not tested for using viral respiratory PCR. If viral respiratory PCR is unavailable or not done, clinicians have used a variety of non-specific laboratory surrogate tests to differentiate influenza from ILI viral pathogens. The differentiation of influenza from viral ILIs was critical during the swine influenza pandemic in 2009–2010, when the sheer numbers of patients made viral-specific diagnosis impossible [4, 5]. Non-specific laboratory parameters abnormalities in the complete blood count (CBC) included leukopenia, relative lymphopenia, and thrombocytopenia alone or in combinations which were predictive of influenza [6, 7]. In addition, a lymphocyte:monocyte ratio of <2 has been used as another surrogate marker for influenza A [8].

Atypical lymphocytes may be a diagnostic clue in a variety of disorders. Excluding drug fevers and some parasitic infections, e.g., babesiosis and malaria, atypical lymphocytes are common in some non-pneumonia viral infections, e.g., Epstein–Barr virus (EBV), cytomegalovirus (CMV), human herpes virus-6 (HHV-6), and acute hepatitis A [9, 10]. In 2009–2010, adults hospitalized with influenza A rarely had atypical lymphocytes. With >5 % of atypical lymphocytes, atypical lymphocytosis is defined but <5 % atypical lymphocytes may also be an important diagnostic clue in some disorders, e.g., drug fever and toxoplasmosis. Different infections result in different intensities of atypical lymphocytes (%). The time

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Table 1 Atypical lymphocytes in hospitalized adults with a viral influenza-like illness (ILI) during the 2015 influenza season

	Patients with atypical lymphocytes	Age (years)	Peak atypical lymphocytes (%)	Appearance of atypical lymphocytes	Duration of atypical lymphocytes (days)
hMPV (4 patients) (with atypical lymphocytes = 1/4)	1	33	1 %	HD #1	1
Rhinovirus/enterovirus (10 patients) (with atypical lymphocytes = 2/10)	1	75	2 %	HD #3	3
	1	91	3 %	HD #1	5
RSV (16 patients) (with atypical lymphocytes = 1/16)	1	90	1 %	HD #2	6
HPIV-3 (5 patients) (with atypical lymphocytes = 3/5)	1	67	3 %	HD #13	4
	1	74	1 %	HD #10	1
	1	83	3 %	HD #1	3

RSV = respiratory syncytial virus; hMPV =human metapneumovirus; HPIV-3 = human parainfluenza virus-3; HD = hospital day

course of the appearance, persistence, and duration of atypical lymphocytes in blood may also be helpful diagnostically, e.g., early in EBV infectious mononucleosis, atypical lymphocytes are not present, but appear two weeks into the infection.

In children, influenza A and B may have atypical lymphocytes, but atypical lymphocytes are rarely present in hospitalized adults with influenza A . During the swine influenza A pandemic in 2009–2010, atypical lymphocytes were not present in hospitalized adults. Accordingly, we wondered if other strains of influenza A circulating during the 2015 influenza epidemic was or was not associated with atypical lymphocytes.

Since influenza A in adults is not associated with atypical lymphocytes, we wondered if the presence of atypical lymphocytes in hospitalized adults with non-influenza viral ILIs might be a useful clue in differentiating influenza A from ILIs if viral PCR is unavailable or pending definitive diagnosis by respiratory viral PCR. There are little data on atypical lymphocytes in ILIs.

Materials and methods

In hospitalized adults during the 2015 influenza A epidemic at our hospital, we used respiratory virus PCR of nasopharyngeal specimens to diagnose influenza and non-influenza respiratory ILI viruses. Since there are no data on atypical lymphocytes in hospitalized adults with ILIs, we retrospectively reviewed the records of 35 hospitalized adults with ILIs diagnosed by viral PCR to determine the presence, intensity, and duration of atypical lymphocytes.

During the 2015 influenza endemic at our hospital, 57 adults with influenza and 35 adults with ILIs similar in terms of age, gender, severity, and comorbidity were admitted for evaluation and treatment. All admitted adult patients with influenza or a viral ILI were tested by respiratory viral PCR of nasopharyngeal specimens. The charts of patients with influenza and ILIs were reviewed specifically for the presence of otherwise unexplained atypical lymphocytes. If atypical lymphocytes were present, the time of their appearance (hospital day), intensity (%), and persistence/duration (hospital days) were recorded.

Results

None of the hospitalized adults with influenza A had atypical lymphocytes. Atypical lymphocytes were present in 7/35 (20 %) hospitalized adults with viral ILIs and most of these patients were elderly (aged 67–91 years). Atypical lymphocytes were present early (<3 days) in 4/7 and late (>3 days) in 3/7 patients. When present, atypical lymphocyte intensity was low (1–3 %). In the seven adults with ILIs with atypical lymphocytes, atypical lymphocytes persisted in some for 3–6 days (Table 1).

None of the influenza A hospitalized adults had atypical lymphocytes. Among the 35 hospitalized adults with viral ILIs, atypical lymphocytes were present in seven patients (hMPV, R/E, RSV, or HPIV-3). Admitted adults with HPIV-3 were more likely to have atypical lymphocytes than other ILI viral etiologies. Atypical lymphocytes in HPIV-3 adults persisted longer into the hospital stay (10–13 days) than other respiratory ILI viruses with atypical lymphocytes.

Discussion

Although this study is limited by relatively small numbers, we conclude that, if atypical lymphocytes are present in hospitalized adults with viral ILIs, the presence of even a few atypical lymphocytes argues against a presumptive diagnosis of influenza A. If present, otherwise unexplained atypical lymphocytes in admitted adults with ILIs are likely due to HPIV-3, which may persist days into hospitalization.

Compliance with ethical standards

Funding None.

Conflict of interest None.

Ethical approval N/A.

Informed consent N/A.

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