Case report

Detection of influenza A(H1N1)pdm09 virus in a patient travelling from Shanghai to Italy in July 2018: an uncommon clinical presentation in a non-seasonal period

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Keywords

Influenza • Surveillance • Travellers' infectious disease • Leukopenia

Summary

Influenza is one of the most common infectious diseases in travellers, especially in those returning from subtropical and tropical regions. In late June 2018 an influenza A(H1N1)pdm09 virus infection was diagnosed in a 36-years-old man, returned from a travel in Shanghai and hospitalized at the Ospedale Policlinico San Martino, Genoa, Italy, with a diagnosis of fever and an uncommon clinical presentation characterised by a persistent leukopenia. Phylogenetic analysis revealed a closeness with influenza A(H1N1)pdm09 strains circulating in the US in May-June 2018.

Prompt recognition of influenza infection led to a proper case management, demonstrating the crucial role of the continuous influenza surveillance programme.

Introduction

Travels are associated with an increased risk of infectious diseases, and influenza is one of the most frequent acquired infectious diseases in travellers [1].

Influenza is characterized by a seasonal pattern only in temperate climates, with a virus circulation usually observed during the cold season, coinciding with a period that lasts from November to March in the Northern Hemisphere, and from April to October in the Southern Hemisphere. In tropical areas, however, influenza virus circulates at low levels all the year round [2]. Trips by air, ship or train facilitate the viral spread, depending of the length of the trip (0-1 infections could occur during a 5 hours flight, 1-3 during an 11 hours flight and 2-5 during a 17 hours flight) and the number of passengers [3, 4]. The short incubation period and the high infectivity of influenza (basic reproduction number - R0 around 1.5) are the key reasons for the high frequency of influenza among travel-related diseases [1].

Fifty million people are estimated to travel to the tropics each year and approximately half of these presents a travel-related health problem [5-8]. The proportion of influenza in travellers returning from subtropical and tropical regions ranges between 5% and 15% as reported by different studies [3, 9-11].

Case report

A 36-years-old man, returned four days earlier from a travel in Shanghai lasted 2 weeks, accessed to the Emergency Department (ED) of Ospedale Policlinico San Martino, Genoa, Italy, on 28th June 2018 with a diagnosis of fever. The main clinical manifestation at the ED access was a hyperpyrexia started two days earlier (maximum body temperature: 39.5°C) responsive to paracetamol; associated symptoms were arthralgia, nausea and vomiting. The physical examination revealed a pharynx hyperaemia without tonsillar hypertrophy; no skin rash, headache or signs of nuchal rigidity were observed. His past medical history wasn't characterized by any disease of note. In the ED a symptomatic therapy with paracetamol (1 g/100 mL) was started.

In Table I the laboratory tests performed during patient's hospitalization are reported. The tests performed at the ED revealed leukopenia (White Blood Cell count: 3 x 10^9/L) and a modest increase in the levels of C-reactive protein (13.6 mg/L), creatinine (1.2 mg/dL), and a low decrease of potassium (3.3 mEq/L) and alkaline phosphatase (ALP, 36 IU/L). Detection of malaria antigens, Epstein-Barr virus (EBV) and cytomegalovirus (CMV) serology, blood culture and urine culture were performed and revealed only a previous EBV infection and a Escherichia coli count in the urine of 106 CFU/

Tab. I. Laboratory tests performed during patient's hospitalization (Emergency Department and Clinical Immunology Unit, Ospedale Policlinico San Martino).

Variable	Reference range	Day 1 (ED)	Day 2 (ED)	Day 5	Day 6	Day 7	Day 8	Day 12
WBCs	4.50-9.80 x 109/L	**3**	**2.72**	**1.76**	**1.76**	**2.35**	**3.16**	4.4
RBCs	4.5-5.9 x 1012/L	5.2	5	4.9	4.6	4.5	4.5	4.9
Hemoglobin	135-175 g/L	144	141	139	**130**	**124**	131	143
Hematocrit	39-51%	44	43.1	41.3	**38.2**	**37.2**	**37.7**	42.1
MCV	80-100 fL	85.3	85.9	83.6	82.9	83.3	83	85.4
MCH	26-32 pg	27.9	28.1	28.1	28.3	27.8	28.9	29
MCHC	320-360 g/L	327	327	337	341	334	348	340
RDW	11.5-14.5%	12.8	12.8	12.2	11.8	11.9	11.8	12.6
Platelet	130-430 x 109/L	143	148	**113**	**114**	131	157	278
Neutrophils	1,80-7,80 x 109/L	2	**1.7**	**0.67**	**0.74**	**1.22**	**1.63**	2.7
Neutrophils	40,0-70,0%		62	**37.9**	41.9	51.8	51.7	61.8
Lymphocytes	1,10-4,80 x 109/L		**0.7**	**0.88**	**0.82**	**0.93**	1.22	1.4
Lymphocytes	19,0-48,0%		24.4	**49.9**	46.9	39.7	38.5	32.2
Monocytes	0,20-0,96 x 109/L		0.4	**0.07**	**0.07**	**0.08**	**0.09**	0.2
Monocytes	3,4-12,0%		**13.2**	4	3.8	**3.2**	**2.8**	4.5
Eosinophils	0,00-0,50 x 109/L		0	0.02	0.03	0.06	0.12	0.1
Eosinophils	0,0-8,0%		0.1	0.9	1.9	2.7	3.8	1.3
Basophils	0,00-0,20 x 109/L		0	0.02	0.03	0.02	0.02	0
Basophils	0,0-1,5%		0.3	1.1	**1.6**	0.7	0.7	0.2
LUC	0,0-4,0%			**6.2**	3.9	1.9	2.4	
Reticulocytes	0,7-1,7 x 100 RBCs				0.3	0.5	0.6	
Creatinine	0,67-1,17 mg/dL	**1.2**	**1.2**	1	1			
Prothrombin time	% (10-13 sec)	73	82	101	101			
Prothrombin time INR	0.80-1.20	**1.24**	1.15	0.99	0.99			
Activated partial thromboplastin time	28,0-40,0 sec	34.8	33.7	33.2	31.9			
Total bilirubin	0.20-1.20 mg/dL	0.46	0.35	0.30	0.27			
Sodium	135-150 mmol/L	136	137	141				
Potassium	3,5-5 mmol/L	**3.3**	3.5	4				
Chloride	90-120 mEq/L		99	102				
Calcium	8,5-11,0 mg/dL		**8.4**	9.1				
Phosphorus	2.5-4.5 mg/dL		3.7	3.8				
Magnesium	1.9-2.5 mg/dL		2.1	2.1				
Glucose	65-110 mg/dL	97	96					
Albumin	34-50 g/L		36.4		40.3			
C-Reactive Protein	0-5 mg/L	**13.6**	**9.6**		3.2	3.2		
ALP	50-116 U/L	**36**	**38**	**30**	**28**			
ALT	0-40 U/L	26	23	18	16			
gGT	11-50 U/L	13		19	16			

WBCs: White Blood Cells count. RBCs: Red Blood Cells count. MCV: Mean Corpuscular Volume. MCH: Mean Cell Hemoglobin. MCHC: Mean Corpuscular Hemoglobin Concentration. RDW: Red cell Distribution Width. LUC: Large Unsustained Cells. ALP: ALkaline Phosphatase. ALT: ALanine aminoTranspherase. gGT: gamma GlutamylTranspherase. INR: International Normalized Ratio.
Values out of range are in bold and underlined.

mL. The latter wasn't treated because asymptomatic. No alterations were visible on the chest X-ray performed on 28th June.

Upon admission at Clinical Immunology Unit, Department of Internal Medicine of Ospedale Policlinico San Martino, the patient was substantially asymptomatic except for a mild non-productive cough. In fact the fever, after the peak at 38.5°C on 28th June at ED, slowly decreased. Leukopenia was still present (from 28th June to the discharge at 10th July) and characterized by low levels of neutrophil granulocytes (0.67 x 10^9/L at the nadir on 2nd July) and also a reduced reticulocyte count was observed from 3rd July (0.3%). Only on-demand therapy with paracetamol and metoclopramide was introduced.

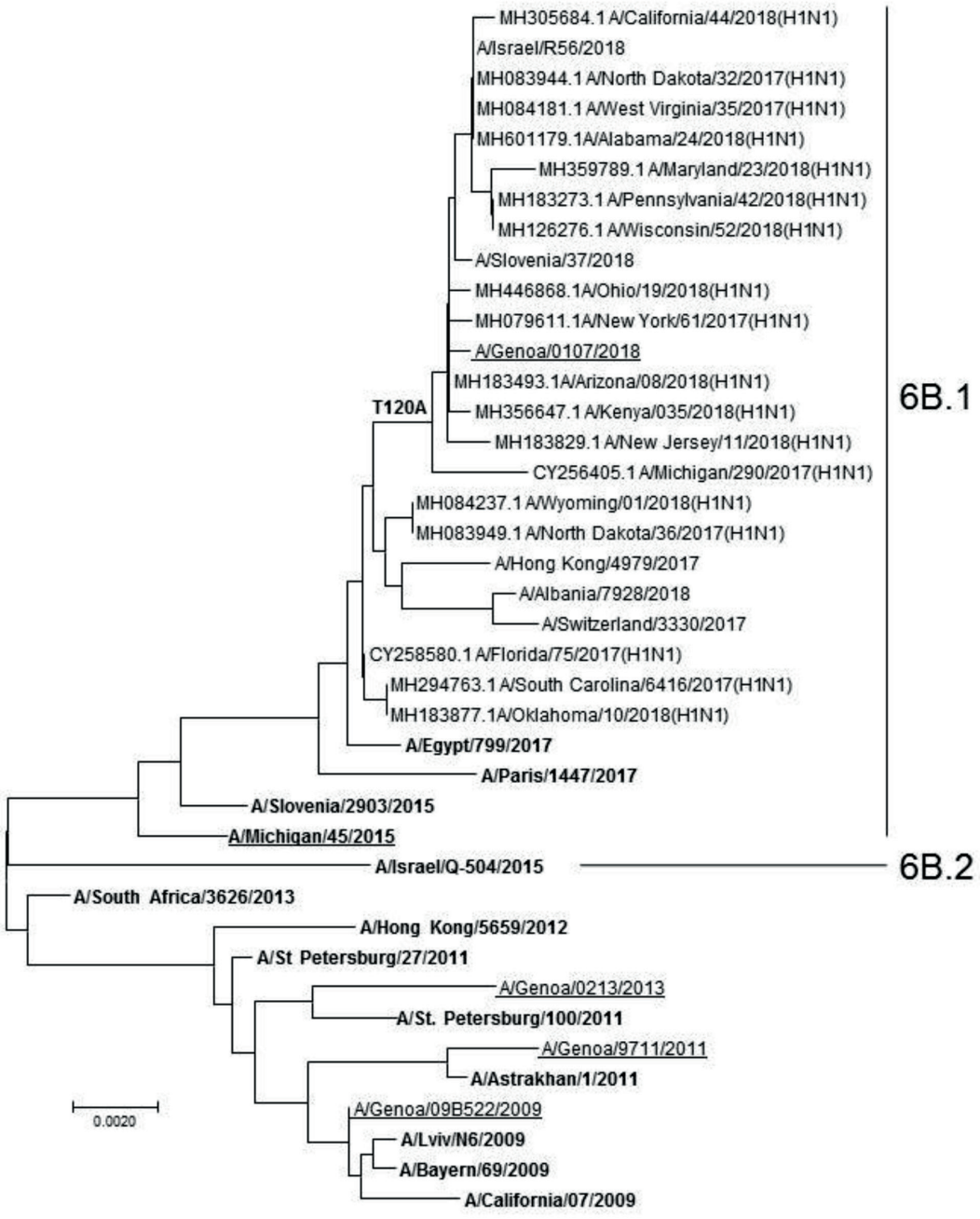
A series of laboratory tests were performed during hospitalization: blood cultures, sputum cultures, detection of Streptococcus pneumoniae and Legionella antigens in urine, parasites tests, detection of malaria antigens in blood samples, serological markers of infection by hepatitis A (HAV), B (HBV) and C (HCV), human immunodeficiency virus (HIV), Zika virus, Parvovirus, Salmonella typhi and paratyphi, Brucella, Proteus,

Schistosoma and Leishmania. Nasopharyngeal swab for respiratory viruses and bacteria was performed for the first time on 2nd July and resulted positive on 4th July, revealing the presence of influenza A(H1N1)pdm09 virus and Haemophilus influenzae.

Antiviral therapy with oseltamivir (150 mg/day) was started on 4th July and the patient was concurrently isolated. The general outcome was good and the patient was discharged at the end of antiviral therapy on 10th July, with a diagnosis of influenza A(H1N1)pdm09 infection and transient neutropenia probably due to infection. The patient received the recommendation to limit contact with people at greater risk (cardiopathic, pneumopathic, elderly in general, immunocompromised people, pregnant women, infants) and to wear the mask until the result of the nasopharyngeal swab performed at the discharge. This last resulted negative three days later, on July 13th.

Phylogenetic analysis of the virus strain were performed as previously described [12] between July and August 2018 and revealed a similarity with viruses isolated in the US in May and June 2018 and characterized by T120A mutation (Fig. 1).

Fig. 1. Phylogenetic analysis of the hemagglutinin (HA) nucleotide sequences from influenza A(H1N1)pdm09 viruses. The phylogeny tree was generated by the neighbor-joining method with 1000 bootstrap replicates. Ligurian strains (underlined), WHO recommended candidate vaccine for 2017/2018 and 2018/2019 Northern Hemisphere influenza season (bold, underlined) and reference strains (bold).



Discussion

Worldwide, in the period June-July 2018 seasonal influenza type A viruses accounted for the majority of detections. A(H1N1)pdm09 prevailed over A(H3N2) viruses. In temperate zone influenza activity was at inter-seasonal levels, whereas in tropical countries of Central America, South America, African region and Asia influenza activity remained low in the same period. In particular virological surveillance in China from week 18 to week 31 of 2018 revealed that influenza subtype A(H1N1)pdm09 virus was the most frequent detected [2]. However, no influenza virus isolation has been notified in Shanghai in the same period [13].

Influenza infection must be taken into account in differential diagnosis in every season and in any patients with acute respiratory disease coming from an intercontinental travel, even though with an atypical clinical presentation. In our case, the diagnosis of influenza infection settled diagnostic doubts, therefore providing the better patient management.

Continuous virological surveillance allows constant monitoring of circulating influenza viruses, representing a key tool for characterization and selection of influenza strains to be included in vaccine composition, as well as for potential detection of new viral strains, including those carrying a pandemic risk.

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Conflict of interest statement

None declared.

Authors' contributions

FB analysed data, wrote, drafted and revised the manuscript. SS, FG and VT advised on analysis, wrote, drafted and revised the manuscript. GB and GG performed virus detection and genotyping and revised the manuscript. BB coordinated laboratory activities. GM and MS coordinated clinical activities and revised the manuscript. AO supervised virological analysis and revised the manuscript. All the authors reviewed and approved the final manuscript.

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