Influenza viruses are among the leading respiratory pathogens in the world. It is estimated that 5% of adults and up to 20% of children develop symptomatic influenza infections every year (1). In addition, influenza has a significant impact on mortality (2). It is well known that influenza viruses display continuous antigenic changes, which account for repeated episodes of infection throughout life. Furthermore, new variants of the virus emerge in the human population every 10 to 40 years, leading to pandemics. Pandemic influenza is characterized by changes in the age distribution of individuals who suffer the severe form of infection and by an increase in the mortality rate (3). Outcomes of influenza infection depend on a series of virus-host interactions, which include the participation of the innate and adaptive immune systems. NK cells play an important role in early antiviral responses through the lysis of infected cells. In experimental models of viral infection, NK cells have been shown to be recruited to the respiratory tract, where they contribute significantly to the reduction of the viral load (4). In addition to their role in the initial control of viral infections, NK cells are able to modulate the development of adaptive immunity (5). Thus, NK cells can exert their protective role directly through the lysis of infected cells or indirectly by modulating the generation of Th1-mediated immune responses through the release of immune interferon.

It is well known that NK cell activity is regulated by a complex array of surface receptors, which are able to elicit inhibitory or activating signals; the integration of these signals determines the activation of NK cells. NK cell receptors (NKR) include, among others, the killer cell immunoglobulin-like receptors (KIRs), the natural cytotoxicity receptors (NCRs) (NKP30, NKP44, and NKP46), and the lectin-like receptors (including NKG2A, NKG2C, and NKG2D) (6).

Several studies have highlighted the importance of NK cells in the initial control of influenza infections. In this regard, it has been reported that NK cell activity is increased upon exposure to influenza-infected cells (7, 8). In addition, viral hemagglutinins, including those of influenza viruses, are recognized by NK cell receptors, mainly NKP46 (7, 9). The role of this receptor has been underscored by experimental studies in which mice lacking NCR1 (NKP46 in humans) developed lethal influenza infections (10). Other studies have shown that influenza virus-infected cells show redistributions of major histocompatibility complex (MHC) class I molecules on their surfaces, which lead to early interactions with NK cells mediated by KIR2DL1 and leukocyte Ig-like receptor 1 (LIR-1); these changes are followed by the recognition of infected cells by the NKP46 receptor (11). Furthermore, it has been reported that the engagement of NKP46 and NKG2D is necessary for the activation of NK cells during their interaction with influenza virus-infected cells (12).

It has been shown that the influenza virus is able to infect NK cells, diminishing their cytotoxic activity and inducing their apoptosis (13, 14, 15). In addition, the exposure of NK cells to viral hemagglutinins or activated virosomes also causes a reduction in NK cell cytotoxic activity, which is independent of NK cell death (16). Furthermore, it has been found that the decreased NK cell activity induced by influenza infection may contribute to bacterial superinfections (17). Studies performed on patients with 2009 pandemic influenza A(H1N1) infection showed a reduction in NK cells in peripheral blood samples (18, 19). Thus, influenza infection seems to be associated with significant changes in the
number and activity of NK cells. However, the possible effects of influenza infection or the in vivo exposure to influenza antigens on the expression levels of different membrane receptors by NK cells have not been determined. In this study, we assessed the numbers of NK and NKT lymphocytes in peripheral blood samples and the expression levels of different membrane receptors by these cells in patients with influenza infection and healthy individuals who were immunized with a seasonal or pandemic vaccine. Our results suggest that severe influenza is associated with significant modifications in the levels of NK and NKT lymphocytes that express the natural cytotoxicity receptors (NCRs) that are able to recognize the influenza virus. It is feasible that these changes contribute to the pathogenesis of influenza infection.

**MATERIALS AND METHODS**

**Subjects and samples.** Twenty-seven healthy volunteers received influenza virus vaccination; 12 were immunized with the (H1N1)pdm2009 vaccine and 15 with the seasonal influenza virus vaccine. Sixteen were female, 11 were male, and their mean age was 29.5 years. In addition, we analyzed a group of patients hospitalized with influenza-like illnesses, eight with moderate infection (all with suspected or confirmed pneumonia but not respiratory distress) and nine with severe disease (pneumonia with acute respiratory distress syndrome [ARDS]). Ten were female, seven were male, and their mean age was 31.7 years. No patient or control with a history of a chronic condition (e.g., diabetes mellitus) or an immune disease (e.g., immunodeficiency or autoimmunity) was included in the study.

Influenza virus screening was carried out by conventional and real-time reverse transcription-PCR using pharyngeal or nasopharyngeal swabs, as described by Gómez-Gómez et al. (20). All cases that showed a positive result corresponded to influenza A(H1N1) virus.

One sample of peripheral blood was obtained from each patient with influenza, and two samples were obtained from each healthy subject, one before and one 2 weeks after their influenza immunization. Data obtained from the first sample from these healthy subjects were used as control data for comparison with data from the samples from the influenza patients. This study was approved by the Bioethical Committee of the School of Medicine, Universidad Autónoma de San Luis Potosí (UASLP), and an informed consent form was signed by all the patients and controls or their close relatives (in the cases of patients with severe infections).

**Flow cytometry analysis.** Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll-Hypaque (Sigma Chemical Co., St. Louis, MO) gradient centrifugation and suspended at 1 × 10^6 cells/ml in RPMI 1640 culture medium. Cells were incubated with saturating amounts of antibodies for 30 min at 4°C. The monoclonal antibodies used for staining were anti-NKp46/CD335-phycocerythrin (PE), anti-NKp44, anti-KIR3DL1, anti-KIR2DL1, and anti-NKG2A (R&D Systems, Minneapolis, MN); anti-CD3-PE-Cy5, anti-CD56-allophycocyanin (APC), anti-CD3-fluorescein isothiocyanate (FITC), and anti-CD8-PE (BD Biosciences, San Jose, CA).

Four-color cell analysis was performed with a FACSAria II flow cytometer. FACSDiva software (BD Biosciences) was used for the computer-assisted analysis, and at least 30,000 cells were acquired from all samples.

**RESULTS**

**Levels of NK and NKT lymphocytes.** We first assessed the possible effects of influenza immunization on the levels of NK cells (CD56^+ CD3^-), CD56^- CD3^- cells (into the lymphocyte gate), and NKT lymphocytes (CD56^- CD3^-) in healthy subjects. We found that seasonal influenza vaccination was associated with significant reductions in the percentages of CD56^- CD3^- lymphocytes (P < 0.01, paired Student’s t test) (Table 1). In addition, no significant variations were observed in the percentages of CD56^- CD3^- NKT cells or T lymphocytes after immunization with either the seasonal or the pandemic vaccine (P > 0.05 in both cases) (Table 1). On the other hand, patients with severe influenza (pneumonia with acute respiratory distress syndrome [ARDS]) showed remarkable and significant increases in the proportions of conventional (CD56^+ CD3^-) NK cells compared to those in healthy controls or patients with moderate influenza infection (pneumonia without ARDS) (P < 0.05 in both cases) (Table 2). In addition, moderate but significant increases in the numbers of CD56^- CD3^- lymphocytes were also detected in patients with influenza and ARDS compared to those in controls or patients with moderate influenza infection (P < 0.05 in both cases) (Table 2). Furthermore, significant decreases in the proportions of T cells were observed in ARDS patients (P < 0.05 compared to those in healthy controls or patients with moderate influenza infection) (Table 2). In contrast, no significant differences were observed in the levels of CD56^- CD3^- cells among the three groups studied (P > 0.05 in all cases) (Table 2).

When the absolute numbers of NK (CD56^+ CD3^-), NKT

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**TABLE 1 Levels of NK and NKT lymphocytes in peripheral blood samples of healthy subjects before and after vaccination against influenza**

| Lymphocyte subset | % (mean ± SD) of cells at the indicated time | (H1N1)pdm2009 vaccine (n = 12) |
|-------------------|------------------------------------------|--------------------------|
|                   | Baseline | 2 wk postimunization | Baseline | 2 wk postimunization |
| NK cells          |          |                      |          |                      |
| CD56^- CD3^-      | 16.5 ± 2.0 | 17.6 ± 1.6 | 22.1 ± 3.2 | 26.2 ± 3.7 |
|                   | 9.8 ± 1.0 | 6.5 ± 0.5 | 11.2 ± 1.0 | 9.8 ± 1.1 |
| NKT cells         |          |                      |          |                      |
| CD56^- CD3^-      | 5.7 ± 0.7 | 5.5 ± 0.7 | 5.9 ± 1.1 | 5.5 ± 1.0 |
| T cells           |          |                      |          |                      |
| CD56^- CD3^-      | 68.0 ± 2.4 | 70.4 ± 1.6 | 60.7 ± 3.2 | 58.6 ± 3.5 |

a Data correspond to the arithmetic means ± SD of the percentages of cells.
b Other lymphocyte subsets, mainly B cells, were included in these percentages.

P < 0.01, baseline compared to 2 weeks postimmunization (paired Student’s t test).
TABLE 2 Levels of NK and NKT lymphocytes in peripheral blood samples of patients with moderate and severe influenza infection (ARDS)\textsuperscript{a}

| Lymphocyte subset | Control (n = 27) | Moderate infection (n = 8) | Severe infection (ARDS) (n = 9) |
|-------------------|-----------------|--------------------------|-------------------------------|
| NK cells          |                 |                          |                               |
| CD56\textsuperscript{+} CD3\textsuperscript{−}   | 19.0 ± 1.8     | 58.0 ± 1.3               | 31.4 ± 4.3\textsuperscript{b} |
| CD56 CD3\textsuperscript{+}   | 10.4 ± 0.7     | 18.9 ± 2.4               | 22.7 ± 2.2\textsuperscript{b} |
| NKT cells         |                 |                          |                               |
| CD56\textsuperscript{−} CD3\textsuperscript{+} | 5.8 ± 0.7      | 6.3 ± 1.7                | 7.0 ± 1.1                     |
| T cells           |                 |                          |                               |
| CD56\textsuperscript{−} CD3\textsuperscript{+} | 64.7 ± 2.0     | 58.0 ± 1.3               | 39.0 ± 5.5\textsuperscript{b} |

\textsuperscript{a} Data correspond to the arithmetic means ± SD of the percentages of cells. 
\textsuperscript{b} P < 0.05, ARDS compared to control or moderate infection.
\textsuperscript{c} Other lymphocyte subsets, mainly B cells, were included in these percentages.

NKp44 and NKp46 expression by NK cells. Then, we assessed the expression levels of the NCRs NKp46 and NKp44 by NK cells in the patients with influenza and the healthy controls. As shown in Fig. 1A, the patients with moderate influenza infection showed levels of CD56\textsuperscript{+} CD3\textsuperscript{−} lymphocytes expressing NKp46 but not NKp44 similar to those of the healthy subjects (P > 0.05, ANOVA). In contrast, the proportions of CD56\textsuperscript{+} CD3\textsuperscript{−} lymphocytes expressing both NKp44 and NKp46 were significantly higher in the patients with moderate infection than in the controls (P < 0.05) (Fig. 1D). On the other hand, the patients with severe influenza infection exhibited diminished numbers of NKp46\textsuperscript{+} NKT cells compared to those in the controls or the patients with moderate influenza infection and increased numbers of NKp46\textsuperscript{−} NKp44\textsuperscript{+} NK lymphocytes compared to those in the healthy subjects (P < 0.01 in all cases) (Fig. 1A and D). In contrast, the expression levels of NKp46 and NKp44 by CD56\textsuperscript{−} CD3\textsuperscript{−} NK cells did not show significant changes after immunization with either the seasonal or the pandemic virus vaccine (P > 0.05 in all cases) (Fig. 1B, C, E, and F). However, the proportions of NKp46\textsuperscript{−} NKp44\textsuperscript{+} NK cells tended to diminish after immunization with the seasonal vaccine (Fig. 1E).

In the case of the coexpression of NKp46 and the inhibitory receptor NKG2A by CD56\textsuperscript{−} CD3\textsuperscript{−} cells, no apparent variations in the proportions of these cells were observed in the patients with influenza infection (moderate or severe) or in the healthy subjects upon seasonal influenza immunization (Fig. 2). However, small but significant increases in the proportions of NKp46\textsuperscript{+} NKG2A\textsuperscript{+} cells were observed in the healthy individuals after immunization with the pandemic virus vaccine (P < 0.05) (Fig. 2F).

In order to explore whether the changes observed in the expression levels of the NCRs by NK cells were due to the infectious process, we obtained an additional blood sample from each of six
of the patients with severe influenza at least 1 year later. As shown in Fig. 3, we detected significant decreases in the percentages of NKp46+ NKp44+ NK cells ($P < 0.05$, Wilcoxon rank sum test), reaching the levels observed in the healthy controls.

**Other NK cell receptors.** When the expression levels of KIRs were analyzed, we observed that a fraction of individuals (9 out of 27) (Fig. 4) who were immunized with the seasonal or the pandemic virus vaccine showed important decreases in the proportions of CD56+CD3− lymphocytes expressing the inhibitory receptor KIR3DL1 (CD158E1), no significant differences were achieved ($P > 0.05$ in both cases) (Fig. 4). Similar results were observed in the case of the other inhibitory receptor (KIR2DL1/DS1) studied (data not shown). Likewise, influenza immunization was not associated with significant changes in the proportions of CD56+CD3− NK cells expressing the KIR3DL1 or KIR2DL1/DS1 receptors (data not shown). In contrast, patients with severe influenza infection, but not those with moderate disease, showed significant increases in the levels of CD56+CD3− NK lymphocytes expressing KIR2DL1 or KIR3DL1 ($P < 0.05$ in both cases) (Fig. 5A and B). Similar results were observed in the case of CD56−CD3− lymphocytes ($P < 0.05$) (Fig. 5E and F); since B lymphocytes show only very low expression levels of KIR molecules (21), it is very likely that these cells correspond mainly to CD56− NK lymphocytes. In addition, in these patients with severe influenza infection, we observed important increases in the levels of NKT cells expressing KIR2DL1 or KIR3DL1 ($P < 0.05$ in both cases) (Fig. 5C and D). Patients with moderate influenza infection also showed modest but significant increases in the percentages of CD56+CD3− NKT cells expressing KIR3DL1 ($P < 0.05$) (Fig. 5D). As in the case of the NCRs, the enhanced expression levels of KIR3DL1 and KIR2DL1/DS1 by CD56+CD3− and CD56−CD3− lymphocytes observed in patients with severe influenza infection returned to the values observed in the healthy controls 1 year after the infectious process (Fig. 3).

Finally, we analyzed the expression of the activation receptor CD161. We found that patients with severe influenza infection...
showed significant reductions in the levels of CD161⁺ NK and NKT cells (data not shown). In contrast, in subjects who were immunized with the (H1N1)pdm2009 vaccine, significant reductions in the percentages of CD161⁺ CD56⁺ CD3⁻ T cells were observed, with no apparent changes in the other cell subsets studied (data not shown).

**DISCUSSION**

Innate immune responses play an important protective role during the initial stages of viral infections. Over the past decade, several studies have addressed the role of NK cells and their receptors involved in the induction of cell killing in influenza virus infections (8, 9, 10, 12, 15, 19, 22, 23). Because NK lymphocytes do not require prior sensitization to exert their lytic effects on infected cells, they may have a key protective role against emergent pathogens or new variants or strains of different viruses. In this work, we have analyzed the levels of NK and NKT cells in peripheral blood samples and the expression levels of different membrane receptors in patients with moderate or severe influenza infection and healthy subjects before and after immunization with a pandemic or seasonal influenza vaccine. We hypothesized that influenza infection and immunization against this virus would increase the levels of NK cells and expression levels of different receptors involved in the induction of these cells or the triggering of their lytic activity. However, we detected only modest effects of influenza immunization on the levels of NK and NKT cells and on the repertoire of the different cytotoxic regulatory receptors studied. In this regard, the small but significant increases in the proportions of NKp46⁺ NKG2A⁺ NK cells observed after immunization with the pandemic vaccine employed in this study seem unexpected, since the presence of NKG2A is associated with inhibitory signals that downregulate the functions of NK cells, including their lytic activity and the release of cytokines (24). In contrast, in the case of double-negative (CD56⁻ CD3⁻) lymphocytes, we have detected an interesting and opposite phenomenon, with important decreases in their expression levels of the inhibitory receptor KIR3DL1 upon influenza immunization. In addition, these immunized patients also showed significant diminutions in the levels of CD56⁻ CD3⁻ lymphocytes expressing this regulatory receptor. All these data suggest that in a small but significant fraction of

**FIG 4** KIR3DL1 expression levels by CD56⁻ CD3⁻ NK cells after and before influenza immunization. The levels of CD56⁻ CD3⁻ KIR3DL1⁺ cells were determined in peripheral blood samples from healthy individuals who were immunized with the seasonal influenza vaccine (A) (n = 15) or the pandemic (H1N1)pdm2009 vaccine (B) (n = 12). Data correspond to the arithmetic means ± SD of the percentages of positive cells. No significant differences were detected in either case (two-tailed Student’s t test).

**FIG 5** Patients with severe influenza infection show enhanced expression levels of KIR2DL1/DS1 and KIR3DL1. Peripheral blood samples were obtained from 27 healthy subjects and 17 patients with influenza infection, 8 with moderate and 9 with severe disease. Then, the percentages of NK cells (CD56⁺ CD3⁻) or NKT lymphocytes (CD56⁺ CD3⁺) expressing KIR2DL1 or KIR3DL1 were determined by flow cytometry analysis. Data correspond to the arithmetic means ± SD of the percentages of positive cells and were analyzed by ANOVA with Bonferroni’s post hoc test. *, P < 0.05; **, P < 0.01; ***, P < 0.001.
In the case of patients with influenza infection, important and significant changes in the levels of NK cells and their repertoire of membrane receptors were observed, mainly in those with more severe disease (pneumonia with ARDS). Thus, the dramatic increases in the levels of CD56<sup>+</sup>CD3<sup>-</sup> cells in peripheral blood samples and the significant enhancement of the proportions of CD56<sup>+</sup>CD3<sup>-</sup> lymphocytes detected in patients with severe disease suggest that a high viral load might modify the levels of NK cells through a direct interaction with them via stimulatory receptors (24, 25) or through the induction of release of cytokines by different cells. In addition, it is possible that the changes in the levels of NK lymphocytes may reflect nonspecific effects of a systemic inflammatory process rather than a specific response to influenza virus. However, our results are in apparent contradiction with those of previous reports showing diminished levels of NK cells in patients with influenza infection (18, 19). It is feasible that the times of blood sampling, the degrees of disease severity, the virus strains involved, and the genetic backgrounds of the patients studied may account, at least in part, for these contrasting results. On the other hand, it is feasible that the significant diminutions in the proportions of T lymphocytes observed in our patients may contribute to the defective adaptive immune responses that have been previously observed in patients with severe influenza infection, who show enhanced susceptibilities to secondary bacterial infections (26).

Since it has been reported that NKp46 interacts with influenza hemagglutinin, this receptor appears to have an important role in the innate immune responses against this virus. In this regard, Gazit et al. reported that NCR1-deficient mice show increased susceptibilities to lethal influenza infection (10). On the other hand, it is of interest that upon engagement of NKp46 and NKp44, NK cells undergo proapoptotic effects that resemble the phenomenon of activation-induced cell death observed in stimulated T lymphocytes. In this regard, it is worth mentioning that our patients with severe influenza infection showed important diminutions in the levels of NKp46<sup>+</sup>NKp44<sup>−</sup> NK cells with concomitant increases in the proportions of NKp46<sup>−</sup>NKp44<sup>+</sup> cells, suggesting that the differential expression levels of these NCRs may influence the fate of NK lymphocytes in patients with severe infection. In addition, it is of interest that in an animal model of viral lung infection, NKp46<sup>−</sup>NKp44<sup>+</sup> NK cells seem to play an important pathogenic role in tissue damage (27).

The patients with severe influenza infection showed additional significant differences in the expression levels of other membrane receptors involved in the regulation of NK cell function. The enhanced expression levels of the inhibitory receptor KIR3DL1 by CD56<sup>+</sup>CD3<sup>-</sup> and CD56<sup>-</sup>CD3<sup>-</sup> cells observed in these patients suggests that this molecule may contribute to the downregulation of NK cell activity during severe infections. A similar phenomenon might occur in the case of NKT lymphocytes. This putative immunosuppressive status might be exacerbated by the reductions in the expression levels of the activating receptor CD161 by NK and NKT cells from patients with severe influenza infection. However, the possible consequences of the enhanced levels of expression of KIR2DL1/DS1 by NK and NKT cells in patients with severe influenza are not easy to predict, since the antibody employed in this study recognizes both isoforms of this receptor, those bearing the long (inhibitory) and the short (stimulating) cytoplasmic tails.

An important issue to elucidate is whether the significant changes in different cell subsets observed by us in patients with severe influenza infection were consequences of the infectious process or were present in them earlier as predisposing factors. We believe that our data from six patients studied during the infection and 1 year later support the first possibility. Thus, it seems very feasible that the virus, along with proinflammatory cytokines, is responsible for the observed changes in lymphocyte subsets in patients with severe infections.

In summary, our data indicate that influenza immunization has only modest and in most cases nonsignificant effects on the levels of NK cells and their repertoire of expression of different activating and inhibitory receptors. In contrast, influenza infection, mainly the severe form of the disease, is associated with important and complex effects on NK cells, which might contribute to the pathogenesis of this condition.

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We declare no conflicts of interest.

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