For more than a century, St. Leo's Church has been the physical, social and spiritual heart of Little Italy. It was the first church in Maryland built specifically for Italian immigrants. In 1880, Archbishop James Gibbons appointed Father Joseph Andreis (a native of Turin and an assistant pastor at St. Vincent de Paul Church), to form a church in the Italian neighborhood where residents could regularly hear Mass in their own language. The cornerstone was laid by Archbishop Gibbons on September 12, 1880, and the church opened the following year.

Designed by E. Francis Baldwin (a prominent local architect who also designed Mount Royal Station and the Maryland Club), the church is an eclectic blend of Italianate and Romanesque elements.

For many years, religious festivals were major events in Little Italy; the two largest were St. Gabriel's and St. Anthony's. During the Baltimore Fire of 1904, members of St. Leo's prayed to St. Anthony to spare their church from fire. St. Anthony's feast day has been celebrated almost annually ever since in thanks to the "miracle" that saved their church.